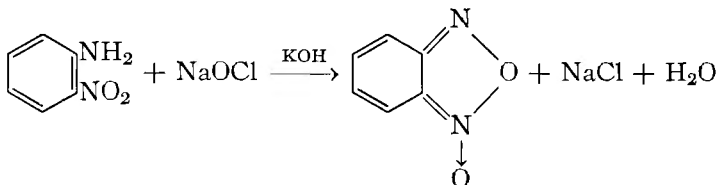


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## BENZOFURAZAN OXIDE



Submitted by F. B. MALLORY.<sup>1</sup>

Checked by T. L. CAIRNS and H. E. SIMMONS.

### 1. Procedure

A. *Sodium hypochlorite solution.* A solution of sodium hypochlorite<sup>2</sup> is prepared immediately before it is to be used. A mixture of 50 g. (1.25 moles) of sodium hydroxide and 200 ml. of water is swirled until the solid dissolves. The solution is cooled to 0°, and 100 g. of crushed ice is added. The flask is then placed in an ice bath, and chlorine gas from a tank is bubbled through the solution until 41 g. (0.58 mole) is absorbed. An excess of chlorine should be avoided. The solution of sodium hypochlorite is kept in the dark at 0° until needed.

B. *Benzofurazan oxide.* A mixture of 21 g. (0.32 mole) of potassium hydroxide and 250 ml. of 95% ethanol in a 1-l. Erlenmeyer flask is heated on a steam bath until the solid dissolves (Note 1). *o*-Nitroaniline (40 g., 0.29 mole) (Note 2) is dissolved in the warm alkali solution. The resulting deep red solution is then cooled to 0°, and the sodium hypochlorite solution from part A is added slowly with good stirring over the course of 10 minutes (Note 3). The flocculent yellow precipitate is collected on a large Büchner funnel, washed with 200 ml. of water, and air-dried. The crude product weighs 36.0–36.5 g. and melts at 66–71° (Note 4). The product is purified by recrystallization from a solution made up from 45 ml. of 95% ethanol and 15 ml. of water. Material insoluble in the hot solvent is removed by filtration, and the hot filtrate is allowed to cool to room temperature. The yield of yellow benzofurazan oxide is 31.6–32.5 g. (80–82%), m.p. 72–73°.

## 2. Notes

1. A small residue of insoluble carbonate may be ignored.
2. Eastman Kodak white label material, melting at 71.5–73.5°, was used.
3. The temperature of the mixture should be kept close to 0° to avoid decomposition of the sodium hypochlorite and prevent formation of tarry materials that occurs at 10–12°. A Dry Ice-acetone bath was found convenient by the checkers.
4. There may be some material that does not melt under 100°, which is not present after recrystallization.

## 3. Methods of Preparation

Benzofurazan oxide is most conveniently prepared by the method herein described, which is adapted from the procedure of Green and Rowe.<sup>3</sup> It has also been reported as an *Organic Syntheses* preparation<sup>4</sup> by way of the pyrolysis of *o*-nitrophenylazide.

Benzofurazan oxide has also been prepared by the oxidation of *o*-nitroaniline with phenyl iodosoacetate.<sup>5</sup> Other methods of preparation are given in reference 4. The hypochlorite oxidation method has been used in the synthesis of various substituted benzofurazan oxides.<sup>6</sup>

<sup>1</sup> California Institute of Technology, Pasadena, California.

<sup>2</sup> A similar procedure is given in *Org. Syntheses*, Coll. Vol. 1, 309 (1941).

<sup>3</sup> Green and Rowe, *J. Chem. Soc.*, **101**, 2452 (1912).

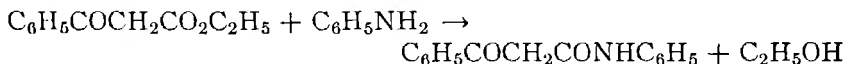
<sup>4</sup> Smith and Boyer, *Org. Syntheses*, **31**, 14 (1951).

<sup>5</sup> Pausacker, *J. Chem. Soc.*, **1953**, 1989.

<sup>6</sup> Gaughran, Picard, and Kaufman, *J. Am. Chem. Soc.*, **76**, 2233 (1954).

## BENZOYLACETANILIDE

(Acetanilide,  $\alpha$ -benzoyl-)



Submitted by C. F. H. ALLEN and W. J. HUMPHLETT.<sup>1</sup>

Checked by MAX TISHLER and R. CONNELL.

## 1. Procedure

A mixture of 105.7 g. (0.55 mole) of ethyl benzoylacetate and 46.6 g. (0.5 mole) of aniline (Note 1) is placed in the dropping funnel *D* (Fig. 1) at the top of the continuous reactor (Notes 2 and 3) after the column has been heated to 135° (transformer set at 80 volts) (Notes 4 and 5). The reactants are then admitted to the column during about 15 minutes (this corresponds to a rate of amide formation of 396–400 g. per hour). Alcohol distills (Note 5) noticeably from the column during the addition and collects in flask *G*. At the completion of the reaction, 100 ml. of xylene is passed through the hot column to rinse out the residual amide (Note 6). An additional 200 ml. of xylene is added to the receiver *C*, and solution is effected by warming. After the solution has been cooled enough to induce crystallization, 100 ml. of petroleum ether (b.p. 35–60°) is added with manual stirring. The mixture is chilled to 15°, then the crystalline product is separated by suction filtration and washed with 300–400 ml. of petroleum ether. The yield is 99–100 g. (83–84%), m.p. 106–106.5° (Note 7). The melting point of this product is not altered by recrystallization from benzene (Notes 8–10).

## 2. Notes

1. Commercial grades of ethyl benzoylacetate and aniline were freshly redistilled before use.

2. The continuous reactor shown in Fig. 1 is of general utility for reactions

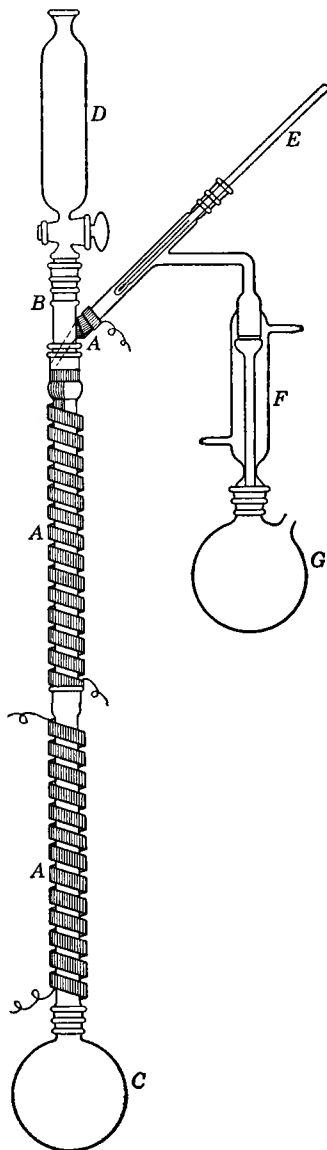


FIG. 1.

that proceed at a rapid rate. Optimum conditions must be determined by experiment for each new product, but a high yield may often be secured. To determine a yield, it is necessary to run a given weight of the components through, rinse the column, and work up the combined products.

3. The reactor is built from stock pieces of glassware having 29/42 and 24/40 standard taper joints. It consists of a column 100 cm. long, of 2 cm. inside diameter, in two 50-cm. sections. The column is packed with  $\frac{1}{8}$ -in. glass helices such as are used for packing distillation columns. The column is heated by two 275-watt flexible heating tapes *A*, 6 ft. long and  $\frac{1}{2}$  in. wide, with lead wires connected to variable transformers, such as the Powerstat or Variac, which are attached to a source of 110-volt power. The heating elements may be covered with asbestos tape if desired. At the bottom of the column is a 500-ml. flask *C* for receiving the product. At the top of the column is a 250-ml. addition funnel *D* (a cylindrical shape is convenient for calibration of volume or for winding with heating tape in instances where melting a solid or heating a solution is required). The addition funnel is connected to the column through a section *B* having a side arm provided with a thermometer *E* and a downward condenser *F* leading to a 500-ml. flask *G*, which has an outlet to the atmosphere for effluent gas.

4. It is always desirable to use a "wet" column; once a column has been used, this condition prevails. It is advantageous to admit a little xylene while regulating the heater, before addition of the reactants.

5. With two 275-watt heating tapes, the required temperature inside the column is secured at a voltage setting of about 80. If alcohol does not distil noticeably during the reaction, the internal temperature is not high enough and the transformer should be adjusted, or more time should be allowed for preheating the column.

6. Part of the product solidifies in the receiver.

7. This compares with 74–76% yield by the batch process.<sup>2</sup>

8. Recrystallization from benzene produces a whiter product in 92% recovery.

9. This procedure may be used to prepare other substituted anilides. If one of the components is a solid, it can be dissolved in an excess of the other. For instance, 46 g. of 2-amino-5-nitroanisole in 285 ml. of hot ethyl benzoylacetate is passed through in 30 minutes, with a transformer setting of 70 volts; then the column is rinsed with 50 ml. of the ester. The product crystallizes in the receiver and is

separated by filtration; the filtrate is used to make up more of the reacting component mixture. The work-up yields 75–76 g. (89%) of amide with the correct melting point (178.5–180°) and color. When the same amide is made by a batch procedure, the yield is only 81% of a product melting at 130–150°. This illustrates the advantage of short time of exposure to heat in the continuous reactor.

10. This reactor has also been used with other types of reactions.

|                                                    | Volt-<br>age | Time,<br>hr. | Mole<br>Ester | Yield,<br>% |
|----------------------------------------------------|--------------|--------------|---------------|-------------|
| Ethyl benzalmalonate (batch) <sup>3</sup>          |              | 18           | 0.63          | 90.8        |
| (cont.)                                            | 65           | 0.5          | 0.69          | 82          |
| 3-Carboxy-4-hydroxyquinoline <sup>4</sup>          | 90           | 0.66         |               | 35          |
| 4-Benzal-2-phenyl-5-oxazolone (batch) <sup>5</sup> |              |              |               | 64          |
| (an azlactone) (cont.)                             | 60           | 0.25         |               | 73          |

### 3. Methods of Preparation

This preparation and oleoyl chloride (p. 66) illustrate the use of the general form of a laboratory-sized continuous reactor.<sup>6</sup> This device has many advantages over the commonly used flasks (batch procedure). In particular, the short time of exposure to heat results in a better quality of product, as shown by less color, fewer side reactions, and better melting point, often unchanged by recrystallization. Furthermore, the unlimited capacity, very short reaction time, and use of concentrated solutions permit a larger output with no increase in size of apparatus and less delay required for removal of solvents.

The continuous reactor is most useful with reactions that take place at a relatively rapid rate. Its wide versatility enables it to be used in many types of reactions. Benzoylacetanilide was selected as an example because it has previously appeared in *Organic Syntheses*.<sup>2</sup>

<sup>1</sup> Eastman Kodak Company, Rochester, New York.

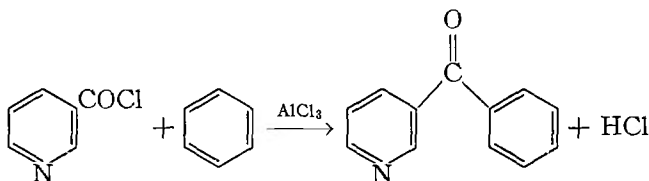
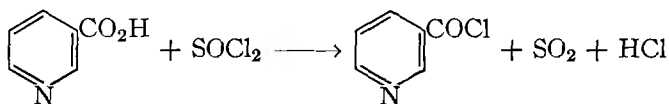
<sup>2</sup> *Org. Syntheses*, Coll. Vol. **3**, 108 (1955).

<sup>3</sup> *Org. Syntheses*, Coll. Vol. **3**, 377 (1955).

<sup>4</sup> Gould and Jacobs, *J. Am. Chem. Soc.*, **61**, 2893 (1939).

<sup>5</sup> *Org. Syntheses*, Coll. Vol. **2**, 490 (1943).

<sup>6</sup> Allen, Byers, Humphlett, and Reynolds, *J. Chem. Educ.*, **32**, 394 (1955).

**3-BENZOYLPYRIDINE****(Ketone, phenyl 3-pyridyl)**Submitted by FRANK J. VILLANI and MARY S. KING.<sup>1</sup>

Checked by MAX TISHLER and MATTHEW A. KOZLOWSKI.

**1. Procedure**

In a 2-l. three-necked flask, fitted with a sealed mechanical stirrer (Note 1), a reflux condenser protected with a calcium chloride tube, and a dropping funnel, is placed 123 g. (1 mole) of nicotinic acid (Note 2). The stirrer is started, and 500 ml. (818 g., 6.9 moles) of distilled thionyl chloride is added in a slow stream over a period of 15–20 minutes (Note 3). After the addition is complete, the mixture is heated on the steam bath with continuous stirring for 1 hour; then the reflux condenser is replaced by one set for downward distillation, and the excess thionyl chloride is removed by distillation at reduced pressure as heating on the steam bath is continued (Notes 1 and 3). After most of the thionyl chloride has been distilled, 200 ml. of anhydrous benzene is added, and the benzene is distilled at reduced pressure. An additional 500 ml. of anhydrous benzene is added, then the flask is fitted with a thermometer and a reflux condenser and is placed in an ice-salt bath. The stirrer is started, and 330 g. (2.5 moles) of anhydrous aluminum chloride is added in portions over a period of 1 hour as the internal temperature is held between 5° and 10°. The ice bath is removed, and the flask is permitted to warm to room temperature and is finally heated under reflux for 6 hours.

The dark red-brown reaction mixture is cautiously poured onto a mixture of 2 kg. of ice and 200 ml. of concentrated hydrochloric acid.

The organic layer is separated and discarded. The acid solution is extracted with three 500-ml. portions of ether (Note 4), which are discarded; then it is treated with 50% aqueous sodium hydroxide until the aluminum hydroxide which first forms redissolves (Note 5). After cooling, the organic material is extracted with five 300-ml. portions of chloroform. The combined chloroform extracts are washed with water, the solvent is removed by distillation on the steam bath, and the product is distilled. The yield of 3-benzoylpyridine (Note 6), b.p. 107–110°/0.3 mm. or 141–145°/4 mm., is 165–175 g. (90–96%),  $n_D^{26}$  1.6088.

## 2. Notes

1. It is convenient to use a sealed stirrer, such as the "Tru-Bore" stirrer, which may be left in the flask during the distillation of thionyl chloride and benzene at reduced pressure; however, the stirrer cannot be left running during this distillation, for it is stopped by the cake of acid chloride hydrochloride. The distillations are accomplished most conveniently if the dropping funnel is removed and replaced by a capillary, and the stirrer is left in place but not running during the distillations.

2. Satisfactory results were obtained with nicotinic acid from either Eastman Organic Chemicals or Matheson, Coleman and Bell.

3. The submitters used thionyl chloride from Hooker Electrochemical Company. It was distilled and collected over a 1° range (78–79°). The first few drops of thionyl chloride are added cautiously as the initial reaction may be quite vigorous. Recovered thionyl chloride may be used for subsequent runs.

4. The ether extractions remove any diphenyl sulfoxide that is formed.

5. About 800–1000 ml. of 50% sodium hydroxide is required.

6. 4-Benzoylpyridine can be obtained by this procedure from isonicotinic acid in yields of 87–90%. This product is recrystallized from hexane, m.p. 72–73°.

## 3. Methods of Preparation

The described method of preparing 3-benzoylpyridine is a modification of that of Wolfenstein and Hartwich.<sup>2</sup> Other methods of preparing this compound are by the addition of phenylmagnesium bromide to



3-cyanopyridine,<sup>3</sup> the addition of 3-pyridyllithium to benzonitrile,<sup>4</sup> the chromic acid oxidation of phenyl-3-pyridylcarbinol,<sup>5</sup> and the decarboxylation of  $\beta$ -benzoylpicolinic acid obtained from quinolinic acid anhydride and benzene.<sup>6</sup>

<sup>1</sup> Schering Corporation, Bloomfield, New Jersey.

<sup>2</sup> Wolfenstein and Hartwich, *Ber.*, **48**, 2043 (1915).

<sup>3</sup> LaForge, *J. Am. Chem. Soc.*, **50**, 2486 (1928).

<sup>4</sup> French and Sears, *J. Am. Chem. Soc.*, **73**, 469 (1951).

<sup>5</sup> Kleipool and Wibaut, *Rec. trav. chim.*, **69**, 1041 (1950).

<sup>6</sup> Bernthsen and Mettegang, *Ber.*, **20**, 1209 (1887).

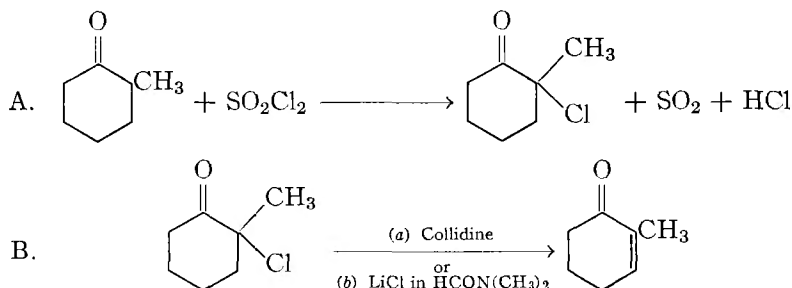
## 2-CHLORO-2-METHYLCYCLOHEXANONE

(Cyclohexanone, 2-chloro-2-methyl-)

and

## 2-METHYL-2-CYCLOHEXENONE

(2-Cyclohexenone, 2-methyl-)



Submitted by E. W. WARNHOFF, D. G. MARTIN, and WILLIAM S. JOHNSON.<sup>1</sup>

Checked by M. S. NEWMAN, G. R. KAHLE, and D. E. REID.

### 1. Procedure

A. *2-Chloro-2-methylcyclohexanone.* A 3-l. three-necked flask, fitted with a sealed mechanical stirrer with glass blade, a dropping funnel, and an outlet tube connected to a gas-absorption trap,<sup>2</sup> is charged with a solution of 224 g. (2.0 moles) of 2-methylcyclohexanone (Note 1) in 1 l. of dry carbon tetrachloride. A solution of 179 ml. (297 g., 2.2 moles) of sulfuryl chloride (Note 2) in 300 ml. of dry carbon tetrachloride is added from the dropping funnel over a 1 hour period with

stirring. The slightly exothermic reaction is moderated by cooling the flask with a bath of water at room temperature. After the addition is complete, stirring is continued for 2 hours. The yellow solution is then washed successively with three 300-ml. portions of water, two 200-ml. portions of saturated sodium bicarbonate solution, and one 200-ml. portion of saturated salt solution, and finally dried over anhydrous magnesium sulfate.

The solvent is removed by distillation through a 15-cm. Vigreux column, first at atmospheric pressure and finally at reduced pressure (water aspirator). The residue is satisfactory for the preparation of 2-methyl-2-cyclohexenone described below (part B). Distillation through the column gives, after a small fore-run, 243–248 g. (83–85%) of colorless 2-chloro-2-methylcyclohexanone, b.p. 94–96°/27 mm.,  $n_D^{25}$  1.4672,  $d_4^{25}$  1.088 (Note 3).

**B. 2-Methyl-2-cyclohexenone.** (a) *Collidine method.* The crude (undistilled) 2-chloro-2-methylcyclohexanone prepared as described above (part A) is transferred to a 1-l. three-necked flask fitted with a stout sealed Hershberg wire stirrer and two efficient reflux condensers, one attached to each side neck; and 290 ml. (266 g., 2.2 moles) of 2,4,6-collidine (Note 2) is added rapidly through one of the condensers with stirring. The flask is heated to 145–150° (bath temperature) with an oil bath until there ensues a sudden exothermic reaction which results in vigorous boiling of residual carbon tetrachloride. The reaction is essentially complete within 1 minute, and the mixture becomes very viscous with suspended collidine hydrochloride. The heating is discontinued, and, as the reaction mixture cools and becomes viscous enough to impede stirring, a total of 500 ml. of benzene is added cautiously (with vigorous boiling) through a condenser in order to maintain fluidity. The collidine hydrochloride is collected by suction filtration on a 10-cm. sintered glass suction filter, then transferred to a beaker, triturated with 300 ml. of benzene, and refiltered. After repetition of this treatment, the weight of residual salt is about 303 g. (96%).

The combined dark-brown filtrates are washed (Note 4) with two 300-ml. portions of 10% hydrochloric acid saturated with sodium chloride, with one 300-ml. portion of saturated sodium bicarbonate solution, and with one 300-ml. portion of saturated salt solution, and finally dried over anhydrous magnesium sulfate. The benzene is removed by distillation through a 15 cm. Vigreux column, and then all material

boiling at 70–97°/56 mm. is collected (Note 5). Fractionation of this material through a 20-cm. heated column packed with steel saddles gives, after a fore-run of benzene, 100–109 g. (45–49% yield from 2-methylcyclohexanone) of colorless 2-methyl-2-cyclohexenone, b.p. 98–101°/77 mm.,  $n_D^{25}$  1.4830–1.4835,  $d_4^{25}$  0.972,  $\lambda_{\max}^{\text{alc}}$  234 m $\mu$  ( $\epsilon$  9660) (Note 6).

(b) *Lithium chloride method.* A 1-l. three-necked flask, fitted with a sealed Hershberg wire stirrer, a thermometer, and a tube leading to a source of nitrogen, is charged with 26 g. of lithium chloride, 250 ml. of dimethylformamide (Note 7) and crude 2-chloro-2-methylcyclohexanone prepared as described above (part A, half-scale) from 112 g. of 2-methylcyclohexanone. The stirrer is started, the air swept out with nitrogen, and the flask immersed in an oil bath maintained at 100°. The temperature of the reaction mixture rises to 100° in about 10 minutes, then to 112° and back to 105° in another 25 minutes. At the end of this time the mixture is cooled, 1-l. each of ether and of 2.5% sulfuric acid is added, and the mixture is stirred for about 4 hours to hydrolyze the dimethylformamide. The aqueous layer is separated, saturated with sodium chloride, and extracted with four 150-ml. portions of ether. These extracts are combined with the original ether layer, washed with saturated sodium chloride solution and saturated sodium bicarbonate solution, and finally dried over anhydrous sodium sulfate. The ether is removed by distillation through a 15-cm. Vigreux column, and then a fraction boiling at 79–107°/28 mm. is collected. Redistillation through a 20-cm. heated column packed with steel saddles gives 47–50 g. (42–45% yield from 2-methylcyclohexanone) of colorless 2-methyl-2-cyclohexenone, b.p. 83–85.5°/35 mm.,  $n_D^{25}$  1.4833–1.4840,  $\lambda_{\max}^{\text{alc}}$  234 m $\mu$  ( $\epsilon$  9680) (Note 6).

## 2. Notes

1. 2-Methylcyclohexanone is available commercially from Aldrich Chemical Company, Milwaukee 12, Wisconsin; Columbia Organic Chemicals, Columbia, South Carolina; or the British Drug Houses Ltd., Poole, England. In the present work it was prepared as follows. A 3-l. three-necked flask, fitted with a Hershberg wire stirrer, dropping funnel, and a thermometer, is charged with a solution of 228 g. (2.0 moles) of 2-methylcyclohexanol (Eastman Kodak Company practical grade) in 1 l. of benzene. A solution of 238 g. of sodium dichromate dihydrate in 1 l. of water containing 324 ml. of concentrated sulfuric

acid and 100 ml. of acetic acid is added from the funnel over a period of 2.5 hours with stirring. The temperature of the reaction mixture is maintained (ice bath) at 10° or slightly below during the addition and also during a 3-hour stirring period after the addition. The aqueous layer is separated, diluted with 250 ml. of water, and extracted with two 300-ml. portions of benzene. These extracts are combined with the original benzene layer, and the whole is washed in sequence with 500 ml. of water, 400 ml. of saturated sodium bicarbonate solution, and 400 ml. of saturated salt solution. After the solution has been dried over anhydrous magnesium sulfate, the benzene is removed by distillation through a 20-cm. Vigreux column. Distillation of the residue through a 20-cm. column packed with steel saddles gives 193–200 g. (85–88% yield) of 2-methylcyclohexanone, b.p. 162.5–163.5°/742 mm.,  $n_D^{25}$  1.4459.

2. Eastman Kodak Company practical grade.

3. The homogeneity of this product has been demonstrated.<sup>3</sup> It is stable for long periods if stored in a brown bottle over a little magnesium oxide.

4. Excessive washing with aqueous solution is avoided as the product has appreciable solubility in water.

5. The dark oily distillation residue (about 72 g.) distils at 140–200°/1 mm. and consists mainly of the dimer of 2-methylenecyclohexanone which can be isolated in 23% yield.<sup>3</sup>

6. On standing, the ketone gradually turns yellow, and the refractive index increases. Redistillation of such material gives pure ketone.

7. Supplied by Matheson, Coleman and Bell.

### 3. Methods of Preparation

The only published method for producing pure 2-chloro-2-methylcyclohexanone is by the action of sulfuryl chloride on 2-methylcyclohexanone.<sup>3</sup> Direct chlorination gives mixtures of the 2- and 6-chloro compounds.<sup>3</sup>

2-Methyl-2-cyclohexenone has been prepared (a) by the action of nitrosyl chloride on 1-methylcyclohexene, followed by dehydrohalogenation with sodium methoxide<sup>4</sup> or sodium acetate,<sup>5</sup> and hydrolysis of the resulting oxime; (b) in an impure condition by several methods;<sup>6–12</sup> (c) by dehydration of the ketol produced by the reaction of methylmagnesium iodide with 1,2-cyclohexanedione;<sup>7b, 13</sup> (d) by bromination of

2-methylcyclohexanone with N-bromosuccinimide, followed by dehydrobromination with pyridine or with 2,4-dinitrophenylhydrazine;<sup>14</sup> (e) and by the present method.<sup>3</sup> The use of lithium chloride in dimethylformamide for the dehydrohalogenation is an adaptation of the method of Holysz.<sup>15</sup>

<sup>1</sup> Department of Chemistry, University of Wisconsin, Madison, Wisconsin.

<sup>2</sup> *Org. Syntheses*, Coll. Vol. 2, 4 (1943).

<sup>3</sup> Warnhoff and Johnson, *J. Am. Chem. Soc.*, **75**, 494 (1953).

<sup>4</sup> Wallach, *Ber.*, **35**, 2822 (1902); *Ann.*, **359**, 303 (1908).

<sup>5</sup> Haworth, *J. Chem. Soc.*, **103**, 1242 (1913).

<sup>6</sup> Godchot and Bedos, *Compt. rend.*, **181**, 919 (1925).

<sup>7</sup> (a) Urien, *Compt. rend.*, **199**, 363 (1934); (b) Butz, Davis, and Gaddis, *J. Org. Chem.*, **12**, 122 (1947).

<sup>8</sup> Mousseron, Jacquier, and Winternitz, *Compt. rend.*, **224**, 1230 (1947).

<sup>9</sup> Mousseron, Winternitz, and Jacquier, *Compt. rend.*, **224**, 1062 (1947).

<sup>10</sup> Dupont, *Bull. soc. chim. Belg.*, **45**, 57 (1936).

<sup>11</sup> Whitmore and Pedlow, *J. Am. Chem. Soc.*, **63**, 758 (1941).

<sup>12</sup> Birch, *J. Chem. Soc.*, **1946**, 593.

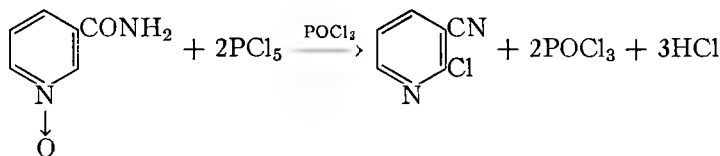
<sup>13</sup> Godchot and Gauquil, *Bull. soc. chim.*, [5]2, 1100 (1935).

<sup>14</sup> Rinne, Deutsch, Bowman, and Joffe, *J. Am. Chem. Soc.*, **72**, 5759 (1950).

<sup>15</sup> Holysz, *J. Am. Chem. Soc.*, **75**, 4432 (1953).

## 2-CHLORONICOTINONITRILE

(Nicotinonitrile, 2-chloro-)



Submitted by E. C. TAYLOR, JR.,<sup>1</sup> and ALDO J. CROVETTI.<sup>2</sup>

Checked by CHARLES C. PRICE and WALTER A. SCHROEDER.

### 1. Procedure

*Caution! This preparation should be conducted in a good hood.*

In a 1-l. round-bottomed flask are placed 85.0 g. (0.62 mole) of nicotinamide-1-oxide<sup>3</sup> and 180.0 g. (0.86 mole) of phosphorus pentachloride (Note 1), and the solids are thoroughly mixed. Two hundred and forty-three milliliters of phosphorus oxychloride is added slowly with shaking. A spiral condenser provided with a drying tube is attached

to the flask which is then placed in an oil bath preheated to 60–70°. The temperature is slowly (20–25 minutes) raised to 100°, during which time the reaction mixture is occasionally shaken. In the range 100–105° the evolution of hydrogen chloride gas increases, and a spontaneous, vigorous refluxing of the phosphorus oxychloride begins. The reaction flask is removed from the oil bath, and the rate of refluxing is controlled by the application of an ice-water bath (Note 2). After the vigorous reaction has subsided (about 5 minutes) the oil bath is replaced, and heating under reflux is continued at 115–120° for 1.5 hours.

After the reaction mixture has been cooled, the excess phosphorus oxychloride is distilled under reduced pressure (80–100 mm.) (0.5–1.0 hour). Near the end of the distillation the product begins to sublime into the still head. The residual dark-brown oil is poured with stirring into an 800-ml. beaker containing 280–300 g. of crushed ice (Notes 3 and 4). The volume of the ice-water mixture is brought to 600 ml. and allowed to stand at 5° overnight. The crude light-brown product is filtered by suction and washed with water.

The solid is suspended in 300 ml. of 5% sodium hydroxide at 15° (Note 5). The mixture is stirred for 30 minutes, and the solid is filtered by suction and washed with water until the filtrates are no longer alkaline. The procedure is repeated, but stirring is continued for 0.75–1.0 hour. After the solid has been filtered by suction, washed, and pressed as dry as possible, it is dried under reduced pressure over phosphorus pentoxide for 12–16 hours.

The solid is transferred to a Soxhlet thimble (45 × 125 cm.) containing a 5-cm. layer of anhydrous sodium carbonate on the bottom (Note 6), and the solid is extracted for 2 to 3 hours with anhydrous ether (700–800 ml.). The total volume of ether is brought to 800–900 ml. The ethereal solution is treated with charcoal and boiled for 10–15 minutes under reflux; then the solution is filtered by suction (Note 7). After evaporation of solvent, 30–33 g. (35–38%) of white 2-chloronicotinonitrile is obtained, m.p. 105–106° (Note 8).

## 2. Notes

1. *To avoid exposure to irritating fumes, the phosphorus pentachloride and oxychloride are handled in the hood. The heating under reflux is also carried out in the hood.*

2. The reaction becomes very exothermic and if uncontrolled there is serious flooding of the condenser. The reaction mixture also becomes dark red to black when the reaction temperature is not controlled.

3. It is difficult to transfer all the oil before solidification starts in the flask. The residual solid is removed by melting on the steam bath and pouring on ice. By repeating this procedure several times, almost all the product can be removed from the flask. Any remaining solid is removed by adding cold water to the flask, breaking the solid with a spatula, and swirling the mixture out of the flask.

4. It is important to stir as rapidly as possible to break the product into small pieces. The beaker should be secured by a large clamp. If the stirring is too slow or the oil is poured too fast, large clumps result which do not solidify completely.

5. Most of the acidic impurities are removed in this step.

6. The sodium carbonate retains any residual moisture and acidic impurities. After the extraction, a brown, gummy, hygroscopic mass remains in the thimble.

7. The checkers found a sintered-glass filter funnel suitable.

8. This product may be recrystallized from ligroin-acetone with 80–85% recovery. Analysis of the product after such recrystallization gave the following analytical results: Calcd. for  $C_6H_3ClN_2$ : C, 51.98; H, 2.16; Cl, 25.63; N, 20.21. Found: C, 52.41; H, 2.39; Cl, 25.43; N, 19.60.

### 3. Methods of Preparation

The preparation reported here is a modification of that reported by Taylor and Croveti.<sup>4</sup> 2-Chloronicotinonitrile has also been prepared by the dehydration of 2-chloronicotinamide<sup>5</sup> and by the Sandmeyer reaction on 3-amino-2-chloropyridine.<sup>6</sup>

<sup>1</sup> Frick Chemical Laboratory, Princeton University, Princeton, New Jersey.

<sup>2</sup> Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois.

<sup>3</sup> *Org. Syntheses*, **37**, 63 (1957).

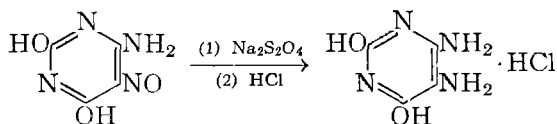
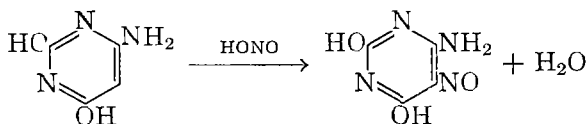
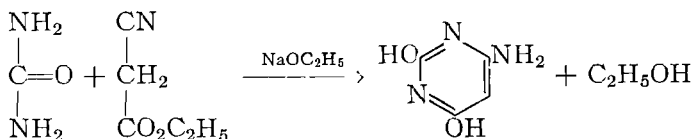
<sup>4</sup> Taylor and Croveti, *J. Org. Chem.*, **19**, 1633 (1954).

<sup>5</sup> Späth and Koller, *Ber.*, **56**, 880 (1923).

<sup>6</sup> von Schickh, Binz, and Schulz, *Ber.*, **69**, 2593 (1936).

## DIAMINOURACIL HYDROCHLORIDE

(Uracil, 5,6-diamino-, hydrochloride)

Submitted by WM. R. SHERMAN and E. C. TAYLOR, Jr.<sup>1</sup>

Checked by T. L. CAIRNS and D. S. ACKER.

## 1. Procedure

Into a 3-l., three-necked flask (Note 1) equipped with a reflux condenser and an efficient stirrer is placed 1 l. of absolute (99.8%) ethanol. To this is added 39.4 g. (1.72 g. atom) of sodium metal, and, after solution is complete (Note 2), 91.5 ml. (97.2 g., 0.86 mole) of ethyl cyanoacetate (Note 3) and 51.5 g. (0.86 mole) of urea are added. The mixture is heated under reflux on a steam bath with vigorous stirring for 4 hours. After about 2 hours, the reaction mixture becomes practically solid, and the stirrer may have to be stopped. At the end of the reaction time, 1 l. of hot (80°) water is added to the reaction mixture, and stirring is resumed. After complete solution has taken place, the stirred mixture is heated at 80° for 15 minutes and is then neutralized to litmus with glacial acetic acid (Note 4). Additional glacial acetic acid (75 ml.) is then added, followed by cautious addition of a solution of 64.8 g. (0.94 mole) of sodium nitrite dissolved in 70 ml. of water. The rose-red nitroso compound separates almost immediately as an expanded precipitate which almost stops the stirrer. After a few minutes the ni-



troso compound is removed by filtration and washed twice with a small amount of ice water. The moist material is then transferred back to the 3-l. flask, and 430 ml. of warm water (50°) is added.

*Caution! This procedure should be conducted in a good hood.* The slurry is stirred while being heated on a steam bath, and solid sodium hydrosulfite is added until the red color of the nitroso compound is completely bleached (Note 5). Then an additional 30 g. of sodium hydrosulfite is added; the light tan suspension is stirred with heating for 15 minutes more and is then allowed to cool. The dense diaminouracil bisulfite is filtered from the cooled solution, washed well with water, and partially dried.

The crude product is readily purified by conversion to its hydrochloride salt. The bisulfite salt is transferred to a wide-mouthed 1-l. flask, and concentrated hydrochloric acid is added until the consistency of the resulting mixture is such as to permit mechanical stirring (100 to 200 ml. of acid). The slurry is heated on a steam bath with stirring for 1 hour (*Hood!*). The tan diaminouracil hydrochloride is filtered on a sintered glass funnel, washed well with acetone, and vacuum-dried over phosphorus pentoxide. The yield of diaminouracil hydrochloride is 104–124 g. (68–81%) (Notes 6 and 7).

## 2. Notes

1. Since the reaction mixture becomes almost solid after nitrosation, one of the necks of the flask should be of large diameter to facilitate removal of the product.

2. The usual precautions must be observed with respect to the hydrogen evolved. The reflux condenser is capped with a drying tube after hydrogen evolution ceases. The sodium ethoxide must be used immediately after its preparation, for it discolors rapidly and in this state leads to an impure product.

3. Eastman Kodak white label, Dow Chemical, and Kay-Fries ethyl cyanoacetate were all used with equal success.

4. Caution must be exercised in the addition of the glacial acetic acid in order to avoid frothing of the hot solution. The frothing becomes most vigorous as the 6-aminouracil begins to precipitate from the solution. The heating and subsequent neutralization assure cyclization of the initially formed cyanoacetylurea to 6-aminouracil. The nitrosation is carried out on the two-phase (solid-liquid) system.

5. The amount of sodium hydrosulfite used depends on its age and quality. The submitters never had to use more than 250 g. per run.

6. The preparation may be interrupted after the nitroso compound has been separated or after the crude bisulfite salt has been isolated. This preparation has been satisfactorily carried out on a scale seven times that given.

7. If placed in a preheated melting-point block, the product melts with decomposition in the range 300–305°. Diaminouracil hydrochloride in 0.1 *N* hydrochloric acid has a well-defined absorption peak at 260 m $\mu$ , log  $\epsilon$  = 4.24. Satisfactory analyses for nitrogen and chlorine are difficult to obtain with this type of compound although good results are obtained for carbon and hydrogen.

### 3. Methods of Preparation

The procedure for the formation of diaminouracil bisulfite is slightly modified from that of Cain, Mallette, and Taylor,<sup>2</sup> which in turn is derived from preparations of Bogert and Davidson,<sup>3</sup> and Traube.<sup>4</sup> The sulfate salt may be formed in lower yield than the hydrochloride described here by dissolving the bisulfite salt in aqueous base and precipitating with sulfuric acid.<sup>3,4</sup> The hydrochloride is appreciably soluble in water, while the sulfate salt is only slightly soluble.

Other methods of reducing the nitroso compound include the use of ammonium sulfide<sup>4</sup> and hydrogenation utilizing Adams catalyst.<sup>5</sup>

Bredereck, Hennig, and Pfeiderer<sup>6</sup> describe a method for the formation of diaminouracil from uric acid which involves acetylation and subsequent hydrolysis of the acetyl derivative. This preparation was attempted on a large scale by the submitters without success (even when the acetylation step was carried out twice on the same material).

<sup>1</sup> University of Illinois, Urbana, Illinois.

<sup>2</sup> Cain, Mallette, and Taylor, *J. Am. Chem. Soc.*, **68**, 1996 (1946).

<sup>3</sup> Bogert and Davidson, *J. Am. Chem. Soc.*, **55**, 1668 (1933).

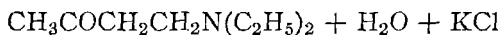
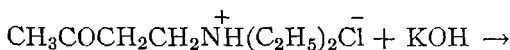
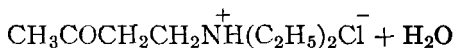
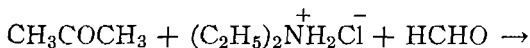
<sup>4</sup> Traube, *Ber.*, **33**, 1371 (1900).

<sup>5</sup> E. C. Taylor, Jr., unpublished results.

<sup>6</sup> Bredereck, Hennig, and Pfeiderer, *Ber.*, **86**, 321 (1953).

## 1-DIETHYLAMINO-3-BUTANONE

(2-Butanone, 4-diethylamino-)

Submitted by ALFRED L. WILDS, ROBERT M. NOWAK, and KIRTLAND E. MCCAULEY.<sup>1</sup>

Checked by WILLIAM S. JOHNSON and DUANE ZINKEL.

## 1. Procedure

In a 3-l. round-bottomed flask equipped with a reflux condenser (Note 1) are placed 176 g. (1.60 moles) of diethylamine hydrochloride (Note 2), 68 g. (2.26 moles) of paraformaldehyde, 600 ml. (8.1 moles) of acetone, 80 ml. of methanol, and 0.2 ml. of concentrated hydrochloric acid. The mixture is heated for 12 hours at a moderate to vigorous rate of reflux (Note 3). The light-yellow solution, in which a small amount of gelatinous solid remains, is cooled, and a cold solution of 65 g. of sodium hydroxide in 300 ml. of water is added. The mixture is extracted with three 200-ml. portions of ether, the combined extracts are washed with two 150-ml. portions of saturated sodium chloride solution, and the washes are re-extracted with two 150-ml. portions of ether.

The combined ether solutions are dried overnight with about 80 g. of anhydrous sodium sulfate, filtered, and then distilled under reduced pressure (5 to 12 mm.) (Note 4) through a 20-cm. asbestos-wrapped Vigreux distilling column, with an efficient water-cooled condenser (Note 5). After the solvent and a small fore-run have been distilled, 150–171 g. (66–75%) of 1-diethylamino-3-butanone is collected as a light-yellow to nearly colorless liquid, b.p. 63–67°/7mm. (75–77°/15mm.),  $n_D^{25}$  1.4300–1.4310. The product may contain a small amount of 1,1-bis(diethylaminomethyl)acetone (the bis-Mannich base), which can interfere with some uses of this product. Refractionation gives relatively pure material, 142–161 g. (62–70%), b.p. 72–75°/10mm.,  $n_D^{25}$  1.4301–1.4307,  $d_4^{25}$  0.8626,  $M_D$  (found) 43.2–43.3,  $M_D$  (calcd.) 43.1 (Note 6).

## 2. Notes

1. Ground-glass joints are desirable.

2. A good grade of commercial diethylamine hydrochloride (Eastman Kodak white label or Matheson, Coleman and Bell) is satisfactory without purification.

3. At first some bumping may occur if the heating is too vigorous; mechanical stirring may reduce this, but does not improve the yield. The submitters found an electrically heated oil bath or a steam bath to be satisfactory, but *not a heating mantle*.

4. If the temperature of distillation is too high, or if a heating mantle is used, decomposition to methyl vinyl ketone may occur. The submitters used an electrically heated oil bath and prefer pressures below 12 mm. to minimize decomposition. A more elaborate fractionating column necessitating a higher bath temperature or prolonged heating is also undesirable. If the material stands more than one or two days before distillation it may decompose.

5. Unless the condenser is efficient, some product will be lost; a Dry-Ice-cooled trap located between the receiver and the pump is recommended.

6. This product gave satisfactory analytical values: Calcd. for  $C_8H_{17}NO$ : C, 67.1; H, 12.0. Found: C, 67.2; H, 11.9. The neutral equivalent of various samples, titrated potentiometrically with standard hydrochloric acid solutions, ranged between 144 and 145 (calcd. 143.2).

## 3. Methods of Preparation

1-Diethylamino-3-butanone has been prepared by the Mannich reaction.<sup>2-6</sup> The present procedure is a modification of that described by Wilds and Shunk.<sup>5</sup>

<sup>1</sup> Department of Chemistry, University of Wisconsin, Madison, Wisconsin.

<sup>2</sup> Mannich, *Arch. Pharm.*, **255**, 261 (1917).

<sup>3</sup> du Feu, McQuillin, and Robinson, *J. Chem. Soc.*, **1937**, 53.

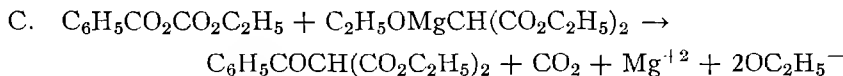
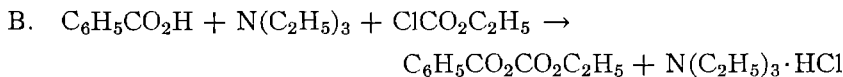
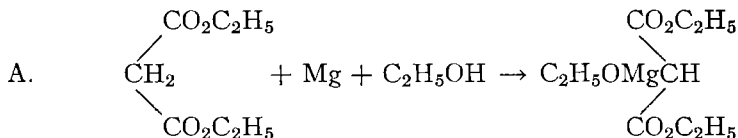
<sup>4</sup> Tuda, Hukusima, and Oguri, *J. Pharm. Soc. Japan*, **61**, 69 (1941) [*C. A.*, **36**, 3154 (1942)].

<sup>5</sup> Wilds and Shunk, *J. Am. Chem. Soc.*, **65**, 469 (1943).

<sup>6</sup> Spaeth, Geissman, and Jacobs, *J. Org. Chem.*, **11**, 399 (1946).

## DIETHYL BENZOYLMALONATE

(Malonic acid, benzoyl-, diethyl ester)

Submitted by JOHN A. PRICE and D. S. TARBELL.<sup>1</sup>

Checked by T. L. CAIRNS and C. L. DICKINSON.

## 1. Procedure

A. *Ethoxymagnesiummalonic ester* (Note 1). In a 250-ml. three-necked flask equipped with a dropping funnel and an efficient reflux condenser fitted with a calcium chloride drying tube are placed 5.0 g. (0.2 g. atom) of magnesium turnings (Grignard), 5 ml. of absolute alcohol (Note 2), 0.2 ml. of carbon tetrachloride, and 6 ml. of a mixture of 32.0 g. (30.2 ml., 0.2 mole) of diethyl malonate (Note 3) and 16 ml. of absolute alcohol. The reaction will proceed in a few minutes and may require occasional cooling before the addition of the remainder of the diethyl malonate solution. The addition should be controlled so that the reaction goes at a fairly vigorous rate. When the reaction mixture has cooled to room temperature, 60 ml. of ether dried over sodium wire is cautiously (Note 4) added. When the reaction again appears to subside, gentle heating by means of a steam bath is begun and continued until nearly all the magnesium has disappeared (Note 5). The alcohol and ether are removed by distillation, first at atmospheric pressure and then at reduced pressure secured with a water pump. To the partially crystalline product is added 60 ml. of dry benzene, and the solvent is again removed by distillation at atmospheric and then reduced pressure (Note 6). The residue is dissolved in 60 ml. of dry ether to await

the completion of the mixed carbonic-carboxylic anhydride preparation.

B. *Mixed benzoic-carbonic anhydride* (Note 7). In a 500-ml. three-necked flask, equipped with a low-temperature thermometer, an efficient sealed stirrer, and an adaptive joint carrying a drying tube and a dropping funnel, is placed a solution of 24.4 g. (0.2 mole) of benzoic acid (Note 8) and 20.2 g. (0.2 mole) of triethylamine (Note 9) in 200 ml. of dry toluene. The solution is cooled below  $0^{\circ}$  by means of an ice-salt mixture, and 21.7 g. (0.2 mole) of ethyl chlorocarbonate (Note 10) is added at such a rate that the temperature does not rise above  $0^{\circ}$  (approximate time for addition is 25–30 minutes). Triethylamine hydrochloride precipitates both during the addition and while the mixture is stirred for 15–25 minutes thereafter.

C. *Diethyl benzoylmalonate*. The dropping funnel used for the chlorocarbonate addition is replaced by another into which the ethereal solution of the ethoxymagnesium compound has been transferred. Approximately 30 ml. of dry ether is used to rinse the flask, and this is also added to the dropping funnel. The ether solution is added to the mixed anhydride with stirring, as the temperature is held at  $-5^{\circ}$  to  $0^{\circ}$ . After the mixture has been allowed to stand overnight and to come to room temperature during this time, it is treated cautiously with 400 ml. of 5% sulfuric acid; then the aqueous solution is separated and extracted once with ether. The two organic layers are combined, washed once with dilute sulfuric acid and then with a concentrated sodium bicarbonate solution until no further benzoic acid is obtained from acidification of the bicarbonate extracts (Note 11). The organic layer is washed with water and dried over anhydrous sodium sulfate. After removal of the sodium sulfate by filtration, the solvent is removed at water-pump pressure from a water bath held at about  $50^{\circ}$ . The resulting product is purified by distillation through a 30-cm. Vigreux column, and the fraction boiling at  $144\text{--}149^{\circ}/0.8$  mm. is collected (Note 12). The yield is 35.8–39.4 g. (68–75%),  $n_D^{25}$  1.5063–1.5066.

## 2. Notes

1. The described procedure is essentially the same as that reported by Lund.<sup>2</sup> A similar preparation has been described by Reynolds and Hauser.<sup>3</sup>

2. A commercial grade is satisfactory for this preparation.

3. Commercial malonic ester was redistilled at reduced pressure to give material with  $n_D^{20}$  1.4047.

4. The ether dissolves the crystalline cake which has formed on cooling. This releases unreacted material and vigorous reaction again sets in.

5. From 6 to 8 hours is required for this operation.

6. The benzene removes any residual alcohol which may interfere with the subsequent acylation.<sup>4</sup>

7. The mixed carbonic anhydride procedure<sup>5-7</sup> has been useful in the preparation of amide linkages and thiol esters. Mixed carbonic anhydrides have successfully acylated, under very mild conditions, the carbanions derived from diethyl ethylmalonate and diethylcadmium.<sup>8</sup> The latter gives as a product the corresponding ketone. Mixed anhydrides derived from acetic and acetylsalicylic acids give results similar to those described here.<sup>8</sup>

8. A good reagent grade of benzoic acid is satisfactory.

9. Redistillation of a commercial grade gave material boiling at 87.0–87.2°.

10. Redistillation of a commercial grade gave material boiling at 90.8–92.0°.

11. If the benzoic acid is not all removed at this stage, it is troublesome during the final distillation.

12. The fore-run, if giving a positive test with ferric chloride reagent, may be redistilled to give increased yields.

### 3. Methods of Preparation

Diethyl benzoylmalonate has been prepared by treatment of the copper derivative of ethyl benzoylacetate with ethyl chlorocarbonate.<sup>9</sup> It has also been obtained by the action of benzoyl chloride on a mixture of malonic ester and sodium ethoxide<sup>10,11</sup> or sodium.<sup>12,13</sup> This compound has been found to be obtainable in higher yields by reaction of benzoyl chloride and the ethoxymagnesium derivative.<sup>14</sup> The present method has been described in a previous communication and is of interest as an illustration of the use of mixed carbonic anhydrides as acylating agents.<sup>8</sup>

<sup>1</sup> Department of Chemistry, University of Rochester, Rochester, New York.

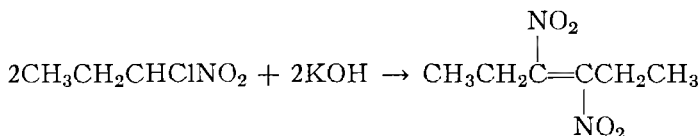
<sup>9</sup> *Org. Syntheses*, Coll. Vol. 2, 594 (1943).

<sup>10</sup> *Org. Syntheses*, 30, 70 (1950).

<sup>14</sup> Riegel and Lilienfeld, *J. Am. Chem. Soc.*, 67, 1273 (1945).

- <sup>6</sup> Vaughan, *J. Am. Chem. Soc.*, **73**, 3547 (1951).  
<sup>6</sup> Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951).  
<sup>7</sup> Wieland and Bernhard, *Ann.*, **572**, 190 (1951).  
<sup>8</sup> Tarbell and Price, *J. Org. Chem.*, **21**, 144 (1956).  
<sup>9</sup> Bernhard, *Ann.*, **282**, 165 (1894).  
<sup>10</sup> Claisen and Falk, *Ann.*, **291**, 72 (1896).  
<sup>11</sup> Bülow and Hailer, *Ber.*, **35**, 934 (1902).  
<sup>12</sup> King, King, and Thompson, *J. Chem. Soc.*, **1948**, 552.  
<sup>13</sup> Borsche and Wannagat, *Ber.*, **85**, 193 (1952).  
<sup>14</sup> Lund, *Ber.*, **67**, 935 (1934).

### 3,4-DINITRO-3-HEXENE



Submitted by D. E. BISGROVE, J. F. BROWN, JR., and L. B. CLAPP.<sup>1</sup>

Checked by JOHN C. SHEEHAN, RICHARD L. WASSON, and HERBERT O. HOUSE.

## 1. Procedure

*This procedure involves the possibility of an explosion and therefore must be conducted with caution.*

In a 1-l. three-necked flask equipped with a mechanical stirrer, a thermometer, and a dropping funnel, and cooled externally with an ice-salt bath, is placed a solution of 118 g. (1.8 moles) of U.S.P. 85% potassium hydroxide (Note 1) in 300 ml. of water. The temperature of the solution is maintained between 0° and 10° (with the addition of ice to the flask if necessary) while 247 g. (205 ml., 2.0 moles) of 1-chloro-1-nitropropane (Note 2) is added from a dropping funnel over a 20-minute period. The cooling bath is removed, and concentrated hydrochloric acid is added dropwise (Note 1) until the momentary green coloration produced by the addition of each drop of acid spreads rapidly throughout the solution (near a pH of 9). The temperature of the solution rises to about 70° with the separation of a deep-green oily layer. Stirring is continued until the reaction mixture reaches room temperature (about 3 hours).

After the green oil has been separated, it is washed with 75 ml. of a warm (*Caution! Note 3*) 20% solution of potassium hydroxide in water



to remove, as its potassium salt, the 1,1-dinitropropane formed as a by-product. The remaining 100–110 g. of oil is diluted with 90 ml. of 95% ethanol, and the green solution is cooled in an ice-salt bath to  $-5^{\circ}$  to  $-10^{\circ}$ . The crystalline product is collected on a cold (Note 4) 5.5-cm. Büchner funnel and washed with two 5-ml. portions of ice-cold alcohol. The yield is 50 g. of impure crystals.

Distillation of the alcoholic filtrate (*Caution! Note 5*) under reduced pressure and in an atmosphere of nitrogen permits the isolation of an additional 8–10 g. of 3,4-dinitro-3-hexene. The blue oil boiling below  $75^{\circ}/20$  mm. is discarded. To the undistilled residue is added 25 ml. of 95% ethanol, the resulting solution is cooled in an ice-salt bath, and the crystals are collected on a cold Büchner funnel and washed with 5 ml. of ice-cold alcohol. The combined crops of crystals are recrystallized from 80 ml. of 95% ethanol. The pure 3,4-dinitro-3-hexene separates as light-yellow needles, m.p.  $31-32^{\circ}$ , weight 50–55 g. (29–32%) (Note 6).

## 2. Notes

1. Although slightly less than an equivalent amount of potassium hydroxide is used, the last of the 1-chloro-1-nitropropane dissolves slowly, and the pH drops sufficiently to allow rapid reaction only after a variable (usually about 3 hours) period of standing. The reaction may also be started by heating one spot on the container with a jet of steam, but it is more convenient and reliable to initiate reaction by cautious addition of acid in the manner described.

2. The 1-chloro-1-nitropropane used was the commercial grade obtained from Commercial Solvents Corporation. The yield was unchanged when a distilled sample, b.p.  $143^{\circ}$ , was used.

3. *The temperature of the potassium hydroxide solution should not be above  $35^{\circ}$  when used.* The submitters report the isolation of 15–20 g. (9–12%) of potassium 1-nitropropylnitronate from the cooled extract. The checkers, having been advised that *this product is a hazardous explosive*, discarded the warm alkaline extract. If 1,1-dinitropropane is not desired (its preparation has been described<sup>2</sup>), it is recommended that it be extracted as its more soluble sodium salt by washing the green oil with sodium hydroxide solution rather than potassium hydroxide solution.

4. It is necessary to keep the Büchner funnel cold since the crystals melt near room temperature. An external cooling jacket for the funnel

can be fabricated from a metal can by cutting a hole in the bottom of the can of such size that it fits high enough on a rubber stopper to allow a tight fit between the rubber stopper and the suction flask. The cooling jacket is filled with crushed Dry Ice. The checkers employed a 60-mm. sintered glass funnel surrounded by a 400-ml. beaker, in the bottom of which was a hole large enough to accommodate a no. 3 rubber stopper surrounding the stem of the funnel.

5. *Distillation behind safety glass in a nitrogen atmosphere appears advisable in view of the nature of polynitro compounds* although the submitters have not had an explosion in the preparation of 3,4-dinitro-3-hexene.

6. 2,3-Dinitro-2-butene may be prepared from 1-chloro-1-nitroethane by the same procedure, in 30% yield. The compound melts at 28–28.5° and has a boiling point of 135°/11 mm. Commercially available 1-chloro-1-nitroethane contains about 10% 1,1-dichloro-1-nitroethane and 2-chloro-2-nitropropane which cannot be separated by distillation, but these impurities do not interfere with the preparation. *Distillation of 2,3-dinitro-2-butene behind safety glass in a nitrogen atmosphere is advisable.* The submitters, in preparing this compound, have had one explosion over a period of ten years.

### 3. Methods of Preparation

The action of a sodium bicarbonate solution or a 10% sodium hydroxide solution on 1-chloro-1-nitropropane will produce 3,4-dinitro-3-hexene. The procedure described here is a modification of that described by Nygaard and Noland.<sup>3</sup>

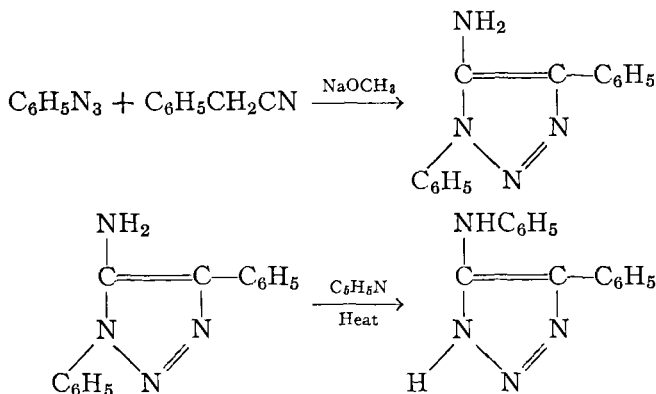
<sup>1</sup> Brown University, Providence, Rhode Island. This work was supported in part by Office of Ordnance Research Contract DA-19-020-ORD-592 at Brown University.

<sup>2</sup> ter Meer, *Ann.*, **181**, 1 (1876); Belew, Grabel, and Clapp, *J. Am. Chem. Soc.*, **77**, 1110 (1955).

<sup>3</sup> Nygaard and Noland (Socony-Vacuum Oil Company), U. S. pat. 2,396,282 (1946) [*C. A.*, **40**, 3126 (1946)].

**1,4-DIPHENYL-5-AMINO-1,2,3-TRIAZOLE****(1*H*-1,2,3-Triazole, 5-amino-1,4-diphenyl-)**

and

**4-PHENYL-5-ANILINO-1,2,3-TRIAZOLE****[1*H*-1,2,3-Triazole, 4-phenyl-5-(phenylamino)-]**Submitted by EUGENE LIEBER, TAI SIANG CHAO, and C. N. RAMACHANDRA RAO.<sup>1</sup>

Checked by T. L. CAIRNS and E. L. MARTIN.

**1. Procedure**

A. *1,4-Diphenyl-5-amino-1,2,3-triazole*. A 500-ml. three-necked flask is equipped with a sealed stirrer, a thermometer well, and a dropping funnel which is protected by a drying tube and has a pressure-equalizing side arm. A mixture of 35.7 g. (0.3 mole) of phenyl azide (Note 1) and 38.6 g. (0.33 mole) of phenylacetonitrile (Note 2) is placed in the flask. The flask is immersed in an ice-water mixture contained in a 1-gal. Thermos flask. After the reaction mixture has cooled to about 2°, a solution of 24.3 g. (0.45 mole) of sodium methoxide (Note 3) in 150 ml. of absolute ethanol is added dropwise during the course of 2 hours. The reaction mixture is then stirred at 2–5° in the ice-water bath for a period of 48 hours (Note 4). After the cooling bath has been removed and the flask allowed to warm spontaneously to room temperature, the mixture is filtered by suction on a sintered glass funnel, and the col-

lected product is washed with three 50-ml. portions of absolute ethanol. The dried product weighs 62–65 g. (88–92%) and consists of white, fine platelike crystals, m.p. 169–171°. Recrystallization from benzene does not alter the melting point (Note 5).

B. *4-Phenyl-5-anilino-1,2,3-triazole*. Six grams (0.025 mole) of 1,4-diphenyl-5-amino-1,2,3-triazole is dissolved in 20 g. of dry pyridine (distilled from solid sodium hydroxide) and heated under reflux for 24 hours (Note 6). The reaction mixture (Note 7) is poured into 1 l. of ice water. The product separates as a slightly yellowish milky oil which is converted to white needle-like crystals by stirring the mixture and scratching the beaker with a glass rod. The product is collected by suction filtration, washed with water, suction-dried, and recrystallized from aqueous ethanol (Note 8). The yield is 5.5–5.6 g. (92–93%) of fine white needle-like crystals, m.p. 167–169° (Note 9), soluble in hot water and ether, but difficultly soluble in benzene.

## 2. Notes

1. Prepared by the method of Lindsay and Allen, *Org. Syntheses*, Coll. Vol. 3, 710 (1955). The phenyl azide used had b.p. 41–43°/5 mm.,  $n_D^{25.5}$  1.5567. The boiling point deviates slightly from that given by Lindsay and Allen, namely 49–50°/5 mm.; however, it agrees fairly well with the other value given by these authors, namely 66–68°/21 mm., and with the values of Darapsky,<sup>2</sup> and the vapor pressure determinations by Carothers,<sup>3</sup> as shown by a plot of  $\log p$  vs.  $1/T$ .

2. The Eastman product was used without purification.

3. Anhydrous sodium methoxide from Matheson Chemical Corporation was used.

4. The yield and purity of the product, i.e., with respect to decreased content of acidic isomer (4-phenyl-5-anilino-1,2,3-triazole), depends upon maintaining a low temperature throughout the entire reaction.

5. The product is essentially pure. 1,4-Disubstituted-5-amino-1,2,3-triazoles are readily isomerized;<sup>4</sup> accordingly, care must be exercised in the recrystallization of such products from solvents. It has been found by experiment that the best practice, in order to avoid isomerization, is to heat the benzene to boiling before addition of the product for recrystallization. Repeated tests have shown that a single careless recrystallization of the product from benzene can increase the content of acidic isomer by as much as 4%. Polar solvents must be avoided.

The purity of the product can be determined <sup>5</sup> by titration in glacial acetic acid, using perchloric acid (in glacial acetic acid) as titrant and methyl violet (0.2 g. of methyl violet in 100 ml. of chlorobenzene) as visual indicator (the first appearance of blue color is taken as the end point).

6. This is more than enough time to allow for the complete irreversible isomerization. The extent of isomerization is checked by removing a small quantity of the reaction mixture, isolating the product by dilution with water, and testing its solubility in dilute potassium hydroxide solution. It should be completely soluble.

7. If any solid material is present, it should be removed by filtration.

8. The acidic isomer can be recrystallized from ethanol without the formation of any of the basic isomer. The checkers used for each gram of product 5 ml. of ethanol and 2.5 ml. of water. After solution of the product, treatment with Darco and filtration, 2.5 ml. of water was added to the hot solution.

9. The purity of the acidic isomer is best determined <sup>5</sup> by titration against sodium methoxide in dimethylformamide, using potentiometric indicator. This test showed the present product to be free of basic isomer.

### 3. Methods of Preparation

The present method is a modification of that first reported by Dimroth.<sup>6</sup> The method of irreversible isomerization in boiling pyridine was first reported by Dimroth<sup>7</sup> for the conversion of 1-phenyl-5-amino-1,2,3-triazole to 5-anilino-1,2,3-triazole.

<sup>1</sup> Department of Chemistry, De Paul University, Chicago, Illinois.

<sup>2</sup> Darapsky, *Ber.*, **40**, 3038 (1907).

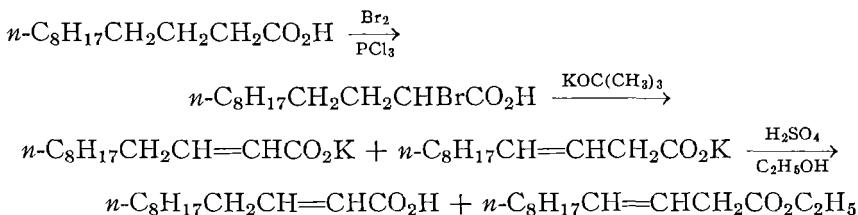
<sup>3</sup> Carothers, *J. Am. Chem. Soc.*, **45**, 1734 (1923).

<sup>4</sup> Lieber, Chao, and Rao, presented at the September 1955 Minneapolis, Minnesota, meeting of the American Chemical Society and submitted for publication to *J. Org. Chem.*

<sup>5</sup> Lieber, Rao, and Chao, *Anal. Chem.*, **29**, 932 (1957).

<sup>6</sup> Dimroth and Werner, *Ber.*, **35**, 4058 (1902).

<sup>7</sup> Dimroth, *Ann.*, **364**, 183 (1909).

**trans-2-DODECENOIC ACID**Submitted by C. FREEMAN ALLEN and MAX J. KALM.<sup>1</sup>

Checked by WILLIAM S. JOHNSON and ALAN D. LOURIE.

**1. Procedure**

*Caution! The bromination step should be carried out in a hood, and appropriate precautions should be employed in handling potassium (Note 1).*

A dry 125-ml. three-necked flask fitted (glass joints) with a sealed mechanical stirrer, an addition funnel, and a reflux condenser capped with a calcium chloride drying tube, is charged with 30.0 g. (0.15 mole) of dodecanoic acid (Note 2) and 0.6 ml. (0.007 mole) of phosphorus trichloride. The mixture is heated at 90–95° (bath temperature), and 8.5 ml. (0.165 mole) of dry bromine (Note 3) is added in one portion with stirring. After stirring for 3 hours at 90–95°, an additional 7.7 ml. (0.150 mole) of dry bromine is added, and the heating and stirring are continued for an additional 7 hours. The dark reaction mixture is then cooled, dissolved in about 100 ml. of carbon tetrachloride, and shaken vigorously with two 100-ml. portions of water. The organic solution is filtered through anhydrous sodium sulfate, and the solvent and excess bromine are removed by distillation at steam-bath temperature and reduced pressure (water aspirator). The residue of bromo acid, which is pale orange in color, is slowly and cautiously added at room temperature to a solution of potassium *tert*-butoxide which has been prepared from 14.7 g. (0.375 g. atom) of potassium (Note 1) and 350 ml. of dry *tert*-butyl alcohol (Note 1), and is contained in a 1-l. flask fitted with a reflux condenser that is protected from moisture with a calcium chloride tube. The resultant thick suspension is heated at gentle reflux for 3–4 hours on a steam bath, then cooled, diluted with about 1 l. of water, and acidified to Congo red with 5 *N* sulfuric acid. The mixture,

containing the precipitated liquid dodecenoic acids, is extracted with two 100-ml. portions of hexane (or a comparable petroleum ether fraction), and the combined hexane solutions are washed with water and dried by filtration through anhydrous sodium sulfate. The hexane is removed by flash distillation, and the residual acid is fractionally distilled through a 2-ft. Podbielniak-type column (Notes 4 and 5). After a small fore-run, the main fraction of dodecenoic acids is collected over a 3° range at about 166–169°/3 mm. The yield is 14–15 g. (47–50%),  $n_D^{25}$  ca. 1.4610 (Note 6).

The distilled mixture of dodecenoic acids is dissolved in 150 ml. of commercial absolute ethanol containing 1.3 ml. of concentrated sulfuric acid and allowed to stand in a stoppered flask for 2 hours at 20°. The solution is diluted with 600 ml. of water, and extracted with two 150-ml. portions of 60–68° petroleum ether. The extracts are washed with water, and percolated through a Kies extraction apparatus (Note 7) consisting of three stages containing, respectively, 9.9 g. of 85% potassium hydroxide (0.15 mole) in 250 ml. of 20% ethanol, 2.5 g. of 85% potassium hydroxide (0.038 mole) in 125 ml. of 20% ethanol, and 125 ml. of water. An additional 250 ml. of petroleum ether is then passed through the extraction apparatus. The three aqueous layers are combined, acidified to Congo red with 5 *N* sulfuric acid, and extracted with petroleum ether. The combined organic layers are washed with water and dried over anhydrous sodium sulfate. The solvent is removed by flash distillation and the residue distilled in a modified Claisen flask. The yield of colorless 2-dodecenoic acid, b.p. 155–158°/3 mm., 127–130°/0.15 mm., is 8–10 g. (27–34%),  $n_D^{25}$  1.4629,  $\lambda_{\max}$  210 m $\mu$  ( $\epsilon$  13,650) in hexane, m.p. 13–18°.

## 2. Notes

1. The precautions for handling potassium and the procedure for preparing anhydrous potassium *tert*-butoxide have already been described.<sup>2</sup>

2. The submitters employed a sample of dodecanoic acid, m.p. 42.5–43°, obtained by fractional distillation of commercial material. The checkers used Eastman Kodak Company yellow-label-grade dodecanoic acid, m.p. 44.5–45°. If a product free of homologous material is desired, purified dodecanoic acid should be used as starting material.

3. The bromine was dried with phosphorus pentoxide and filtered into the addition funnel through a plug of glass wool.

4. A simplified Podbielniak column<sup>3</sup> was employed. Other columns of comparable efficiency should be suitable.

5. This distillation is of importance; if omitted, the final 2-dodecenoic acid is difficult to purify.

6. The mixture of dodecenoic acids exhibited  $\lambda_{\max}$  at 210 m $\mu$  ( $\epsilon$  11,980) in hexane. From the extinction coefficient (13,650) for the pure 2-isomer and that (about 1000) for the 3-isomer, it is calculated that this mixture contains about 13% of the latter. A small amount of dodecenoic acid also appears to be present.

7. The Kies extraction apparatus<sup>4</sup> is useful in minimizing emulsion formation. The checkers performed the countercurrent extractions successfully in separatory funnels. The solutions must be mixed by mild rocking of the funnels; otherwise serious emulsions will be produced.

### 3. Methods of Preparation

Higher-molecular-weight normal 2-alkenoic acids have been prepared in poor yields by the Doebner condensation of aldehydes with malonic acid,<sup>5-7</sup> and by the Reformatsky reaction of aldehydes with ethyl bromoacetate followed by dehydration.<sup>8</sup> The  $\alpha$ -iodo acid, prepared from the bromo acid, has been dehydrohalogenated with potassium hydroxide in ethanol,<sup>9</sup> but large quantities of the  $\alpha$ -hydroxy acid are formed as a by-product which is difficult to separate in some instances. The present procedure is an adaptation of a published method.<sup>5</sup>

<sup>1</sup> University of California, Berkeley, California.

<sup>2</sup> *Org. Syntheses*, **30**, 18 (1950).

<sup>3</sup> Cason and Rapoport, *Laboratory Text in Organic Chemistry*, p. 237, Prentice-Hall, New York (1950).

<sup>4</sup> Kies and Davis, *J. Biol. Chem.*, **189**, 637 (1951).

<sup>5</sup> Cason, Allinger, and Sumrell, *J. Org. Chem.*, **18**, 850 (1953).

<sup>6</sup> Lauer, Gensler, and Miller, *J. Am. Chem. Soc.*, **63**, 1153 (1941).

<sup>7</sup> Zaar, *Ber. Schimmel and Co., Akt.-Ges.*, 299 (1929) [*C. A.*, **24**, 2107 (1930)].

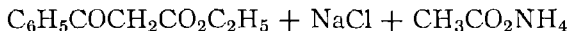
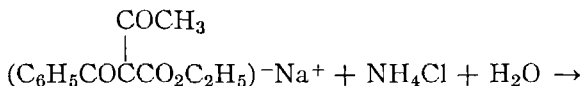
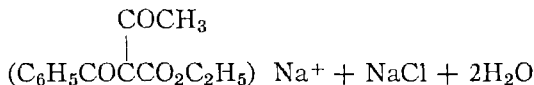
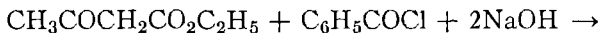
<sup>8</sup> Cason and Sumrell, *J. Org. Chem.*, **16**, 1181 (1951).

<sup>9</sup> Meyers, *J. Am. Chem. Soc.*, **73**, 2100 (1951); Sweet and Estes, *J. Org. Chem.*, **21**, 1426 (1956).



## ETHYL BENZOYLACETATE

(Acetic acid, benzoyl-, ethyl ester)

Submitted by J. M. STRALEY and A. C. ADAMS (*Deceased*).<sup>1</sup>

Checked by MAX TISHLER and M. A. KOZLOWSKI.

## 1. Procedure

In an open 3-l. three-necked flask, equipped with an efficient mechanical stirrer (Note 1) and two dropping funnels, are placed 500 ml. of water, 250 ml. of technical naphtha boiling at 95–110°, and 195 g. (1.5 moles) of freshly distilled ethyl acetoacetate. The mixture is cooled to 5° with a water-ice bath, and 65 ml. of 33% sodium hydroxide solution (33 g. sodium hydroxide in 100 g. solution) is added. As the temperature is maintained below 10° (Note 2) and the pH near 11 (Note 3), the mixture is stirred vigorously (Note 1), and there are added simultaneously from the two dropping funnels 230 g. (1.62 moles) of benzoyl chloride and 270 ml. of 33% sodium hydroxide solution. This addition should be made during about 2 hours. After addition is complete, the cooling bath is removed, and the mixture is allowed to come to room temperature. In order to insure complete reaction, the mixture is finally brought to 35° during about 1 hour. The stirrer is then stopped, and the aqueous layer is separated and placed in a 2-l. Erlenmeyer flask (Note 4).

To the mixture is added 80 g. of technical ammonium chloride; then it is stirred slowly overnight. The specific gravity is brought to 1.13 by the addition of about 90 g. of sodium chloride, after which the mixture is transferred to a separatory funnel. About 10 ml. of benzene is used to rinse the flask and is added to the separatory funnel. The aqueous

layer is withdrawn (Note 5), and the oil is washed three times with 100-ml. portions of cold water.

An additional 40 ml. of benzene is added (to accomplish drying on distillation), and the product is distilled under reduced pressure, using a short still head with no fractionating column (Note 6). The yield of ethyl benzoylacetate, b.p. 145–150°/12 mm., is 197–203 g. (68–71%) (Note 4).

## 2. Notes

1. Good stirring is essential. Slow stirring results in low yields.
2. Temperatures above 10° did not result in consistently good yields.
3. Lower *pH* did not give good yields. The *pH* was checked by means of filter paper, which had been dipped in an alcoholic solution of alizarin and then dried.
4. The naphtha layer may be used without further treatment for the next run. Yields of 76% have been obtained on such a second run without making allowance for recovered ethyl acetoacetate. Distillation of the naphtha layer together with the fore-run from the final distillation of ethyl benzoylacetate yields 11–14 g. of recovered ethyl acetoacetate and about 235 ml. of naphtha.
5. As high as 62 g. of benzoic acid has been recovered by acidification of the aqueous layer.
6. The chief impurity in the crude ester is a high-boiling material of unknown composition.

## 3. Methods of Preparation

The methods of preparation have been listed in two earlier volumes.<sup>2,3</sup> The present method, which is an adaptation of a process found in German documents,<sup>4</sup> is a shorter, more simple procedure which does not require use of dry solvent or metallic sodium.

<sup>1</sup> Research Laboratories, Tennessee Eastman Company, Kingsport, Tennessee.

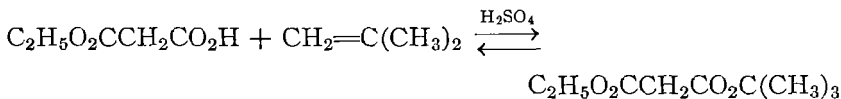
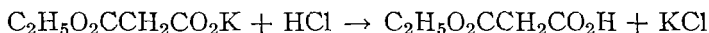
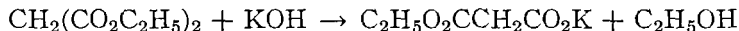
<sup>2</sup> *Org. Syntheses*, Coll. Vol. 2, 266 (1943).

<sup>3</sup> *Org. Syntheses*, Coll. Vol. 3, 381 (1955).

<sup>4</sup> B.I.O.S., *Final Rept.* 1149, 115.

## ETHYL *tert*-BUTYL MALONATE

(Malonic acid, ethyl *tert*-butyl ester)



Submitted by R. E. STRUBE.<sup>1</sup>

Checked by WILLIAM S. JOHNSON and DUFF S. ALLEN, JR.

### 1. Procedure

A 2-l. three-necked flask, equipped with a sealed stirrer, a dropping funnel and a reflux condenser provided with a calcium chloride drying tube, is charged with 100 g. (0.625 mole) of diethyl malonate (Note 1) and 400 ml. of commercial absolute ethanol. Stirring is started, and a solution of 35 g. of potassium hydroxide pellets (Note 2) in 400 ml. of commercial absolute ethanol is added at room temperature during a period of 1 hour. A white crystalline precipitate forms during the addition, and, after all the hydroxide has been added, stirring is continued for an additional 2 hours. After the mixture has stood overnight, it is heated to boiling on the steam bath and filtered while hot with suction (Note 3). Precipitation of the potassium ethyl malonate is completed by cooling the filtrate in an ice bath. The salt is collected by suction filtration, washed with a small amount of ether, and dried under reduced pressure at room temperature. An additional amount of the potassium salt is obtained by concentrating the mother liquors on the steam bath to about 100–125 ml. The total yield is 80–87 g. (75–82%).

A 250-ml. three-necked flask provided with a stirrer, a dropping funnel, and a thermometer is charged with 80 g. (0.470 mole) of potassium ethyl malonate and 50 ml. of water. The mixture is cooled to 5° with an ice bath, and 40 ml. of concentrated hydrochloric acid is added over a 30-minute period while the temperature is maintained below 10°. The mixture is filtered with suction, and the precipitate of potassium chloride washed with 75 ml. of ether. The aqueous layer of the filtrate is separated and washed with three 50-ml. portions of ether. The com-

bined ether solutions are dried over anhydrous magnesium sulfate; then most of the solvent is removed by distillation at atmospheric pressure, and the remainder under reduced pressure. Finally, the liquid residue of monoethyl malonate is dried at 50°/1 mm. for 1 hour. The yield is 58–62 g. (93–100%).

A 500-ml. Pyrex heavy-walled, narrow-mouthed pressure bottle is charged with 100 ml. of ether and 3.5 ml. of concentrated sulfuric acid. The solution is cooled with an ice bath to 5°, and 56 g. (0.424 mole) of monoethyl malonate and approximately 60 ml. (about 0.75 mole) of isobutylene (Note 4) are added. The bottle is immediately closed with a rubber stopper, which is clamped or wired in place, and is shaken mechanically at room temperature overnight (Note 5). The bottle is chilled in an ice-salt bath and then opened. The reaction mixture is poured into a 1-l. Erlenmeyer flask containing a cooled solution of 50 g. of sodium hydroxide in 200 ml. of water and 200 g. of ice. The mixture is swirled a few times and then transferred to a separatory funnel (Note 6). The layers are separated, and the aqueous portion is extracted with two 75-ml. portions of ether. The organic layers are combined and dried over anhydrous magnesium sulfate. The solution is concentrated in a 125-ml. round-bottomed flask (Note 7) and distilled at reduced pressure through a 10-cm. Vigreux column. The fraction distilling at 98–100°/22 mm. or 107–109°/24 mm. is collected. The yield is 42–47 g. (53–58%),  $n_D^{25}$  1.4128,  $n_D^{23}$  1.4142.

## 2. Notes

1. Diethyl malonate as supplied by the Eastman Kodak Company (white label grade) or by Abbott Laboratories may be used without further purification.

2. Potassium hydroxide (85% minimum assay) obtained from the Mallinckrodt Chemical Works is satisfactory.

3. A steam-heated Büchner or a warmed sintered glass funnel is recommended.

4. Technical grade isobutylene supplied by Matheson Company was used. The isobutylene gas is liquefied by passage into a large test tube immersed in a Dry Ice-acetone bath.

5. For convenience, the reaction was carried out overnight. The reaction time may probably be shortened (compare the preparation of di-*tert*-butyl malonate<sup>2</sup>).

6. The mixture may be filtered, if necessary, to remove ice.

7. Since traces of acid will decompose the ester during the distillation, it is essential to wash the distillation apparatus carefully with a sodium hydroxide solution before rinsing and drying. The addition of some potassium carbonate or magnesium oxide before distillation is recommended (see Note 5 of reference 2).

### 3. Methods of Preparation

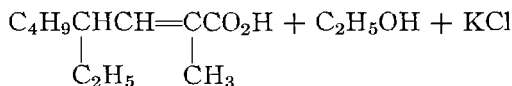
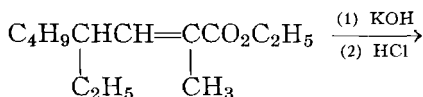
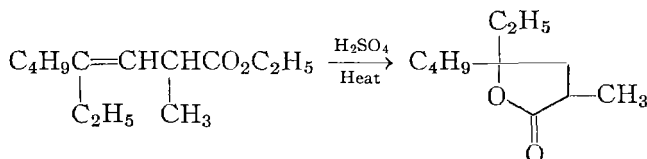
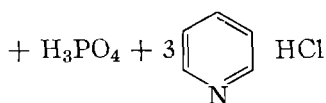
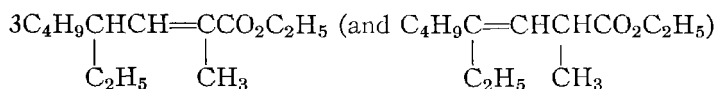
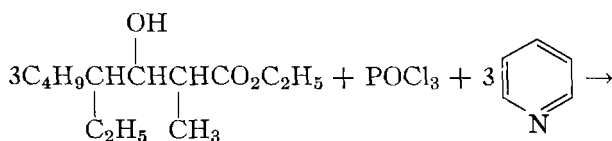
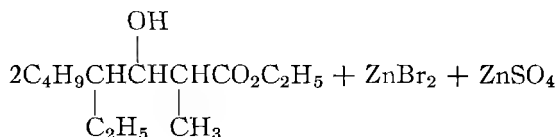
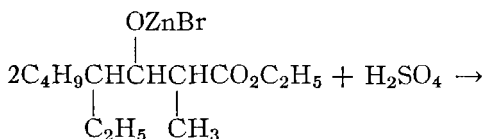
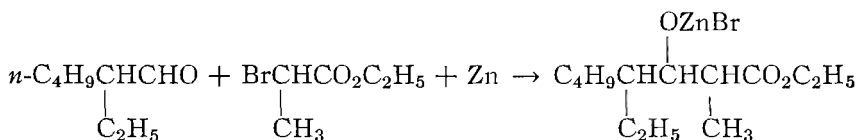
Ethyl *tert*-butyl malonate has been prepared by adding *tert*-butyl acetate and ethyl carbonate to sodium triphenylmethyl,<sup>3</sup> and from ethyl malonyl chloride and *tert*-butyl alcohol.<sup>4</sup> The present procedure is an adaptation of that for the preparation of di-*tert*-butyl malonate.<sup>2</sup>

<sup>1</sup> Department of Chemistry, Research Division, The Upjohn Company, Kalamazoo, Michigan

<sup>2</sup> *Org. Syntheses*, **34**, 26 (1954)

<sup>3</sup> Hauser, Abramovitch, and Adams, *J. Am. Chem. Soc.*, **64**, 2714 (1942)

<sup>4</sup> Breslow, Baumgarten, and Hauser, *J. Am. Chem. Soc.*, **66**, 1287 (1944)

**4-ETHYL-2-METHYL-2-OCTENOIC ACID****(2-Octenoic acid, 4-ethyl-2-methyl-)**

## 1. Procedure

A 3-l. three-necked flask is equipped with a mercury-sealed mechanical stirrer prepared from tantalum wire, a condenser arranged for distillation, and a 500-ml. pressure-equalizing dropping funnel. The flask is heated on a steam cone, and a slow stream of nitrogen is introduced from a cylinder through a line connected to the top of the dropping funnel. To the flask are added 98.1 g. (1.50 g. atoms) (Note 1) of freshly sandpapered zinc foil which has been cut into narrow strips and rolled loosely, and 750 ml. of thiophene-free benzene previously dried over sodium. To dry the apparatus and contents, 175–200 ml. of benzene is slowly distilled with stirring. Heating is interrupted, and the condenser is quickly arranged for reflux. A U-tube just closed with mercury is attached to the top of the condenser, and nitrogen flow is adjusted so that it bubbles slowly through the mercury. The benzene is heated once again to reflux, and a solution of 64.1 g. (0.50 mole) of 2-ethylhexanal (Note 2) and 271.5 g. (1.50 moles) of ethyl  $\alpha$ -bromopropionate (*Caution! Note 3*) in 500 ml. of dried benzene is placed in the dropping funnel. The first 50 ml. of the solution is added to the flask at once. Usually reaction begins immediately, as evidenced by darkening of the zinc surface and clouding of the solution, but in some cases as much as 15 minutes elapses before the start of reaction. When the reaction has started, the remainder of the aldehyde-bromo ester solution is added during 1 hour, with stirring, as the solution is maintained under reflux. After addition is complete the mixture is heated for an additional 2 hours under reflux, and then cooled to room temperature.

The nitrogen line is removed, and to the solution is added 750 ml. of 12 *N* sulfuric acid; the resulting mixture is stirred vigorously for 1 hour, and then decanted into a 3-l. separatory funnel. After the two phases have separated, the lower aqueous layer is drawn off into a 3-l. separatory funnel containing 1 l. of water which has been used to wash the reaction flask, and the diluted mixture is extracted twice with 350-ml. portions of benzene which have also been employed to rinse the reaction flask. The original organic layer and the combined benzene extracts are kept separate and are washed successively with 500-ml. portions of water, saturated sodium bicarbonate solution, and again with water. The two organic portions are now combined, allowed to stand over anhydrous sodium sulfate until clear, then transferred

to a 2-l. distilling flask, from which solvent is distilled at atmospheric pressure, last traces under aspirator pressure. The residue remaining in the flask weighs 150–165 g. (Note 4) and is dehydrated without further purification.

To the residue which contains the crude hydroxy ester there is added 710 g. of pyridine (commercial reagent, c.p. grade), and the mixture is cooled to about 5° in an ice bath. To the cooled solution is added slowly with vigorous swirling 155 g. of phosphorus oxychloride (commercial reagent, c.p.); white crystals form almost immediately. The mixture is allowed to stand 8 hours at room temperature and is finally heated for 1.5 hours on the steam bath (Note 5). It is then cooled to room temperature and decanted into a 5-l. separatory funnel containing 1.25 kg. of cracked ice. Crystals that remain in the flask are decomposed with an additional 125 g. of ice. The flask is rinsed with 1.5 l. of water, and then with 400 ml. of hexane. These washes are added to the material in the separatory funnel. After the two layers have been shaken together thoroughly and then separated, the aqueous phase is extracted with two additional 400-ml. portions of fresh hexane. The three hexane extracts are not combined, but are washed in turn with two 500-ml. portions of 2 *N* hydrochloric acid to remove pyridine. Excess hydrochloric acid is removed by washing with three 200-ml. portions of water to pH 4. The clear amber-colored solution is dried over anhydrous sodium sulfate, and solvent is removed by distillation as before. The residue, which weighs 120–135 g. and consists mainly of ethyl 4-ethyl-2-methyl-2-(and-3-)octenoates, is not distilled but is heated with sulfuric acid to convert the  $\Delta^3$ -isomer to  $\gamma$ -lactone (Notes 6, 7, and 8).

To the residue is added 600 ml. of ethylene glycol, followed by 40 ml. of concentrated sulfuric acid. The resulting mixture is heated under vigorous reflux for 20 hours, and then cooled and transferred to a 2-l. stainless-steel or copper flask. To this material is added a solution prepared from 325 g. of potassium hydroxide, 300 ml. of water, and 300 ml. of 95% ethanol. The resultant solution is heated under reflux for 1 hour, and then cooled and transferred to a 5-l. separatory funnel, where it is diluted with 3 l. of water and acidified with 600 ml. of concentrated hydrochloric acid. The organic liquid which separates is diluted with 300 ml. of hexane and separated from the aqueous layer, which is extracted three additional times with 300-ml. portions of hexane. The hexane extracts are washed to pH



4 with three 300-ml. portions of water, and then combined and dried over anhydrous sodium sulfate. For removal of solvent by flash distillation, a 150-ml. round-bottomed flask, equipped with a ground joint attached to a distillation head and side tubulature attached to a dropping funnel, is heated by an oil bath whose temperature is maintained at 130–140°. After all the solution has been added at about the rate of distillation, the dropping funnel is replaced by a capillary, and the last of the solvent is removed at reduced pressure furnished by a water pump. The flask is finally attached to an efficient fractionating column (Note 9), and the residue of mixed  $\alpha,\beta$ -unsaturated acid and  $\gamma$ -lactone is distilled carefully at reduced pressure. After 1–5 g. of fore-run, there are obtained 25–28.5 g. (27–31%) of 4-ethyl-4-hydroxy-2-methyloctanoic acid,  $\gamma$ -lactone, b.p. 118–121°/5.0 mm.,  $n_D^{25}$  1.4469–1.4473 (Note 10), 2–3 g. of intermediate, and 27.5–32 g. (30–35%) of 4-ethyl-2-methyl-2-octenoic acid, b.p. 140–143°/5.0 mm.,  $n_D^{25}$  1.4613–1.4625 (Note 11).

## 2. Notes

1. The yield in this reaction is improved by an excess of zinc and bromoester relative to aldehyde. The present ratio of zinc:bromoester:aldehyde (3:3:1) gives 87% of intermediate  $\beta$ -hydroxy ester; when the ratio is reduced to 2:3:1, the yield is lowered to about 68%.

2. Commercially available 2-ethylhexanal (Eastman practical grade) is purified by fractional distillation; b.p. 163–163.2°/atm.,  $n_D^{25}$  1.4133. Other aldehydes are conveniently prepared by the Rosenmund reduction.<sup>2</sup> If the aldehyde is relatively unstable toward autoxidation,<sup>3</sup> a catalytic amount (0.5–1.0 g.) of hydroquinone is added with the aldehyde-bromo ester solution.

3. Ethyl  $\alpha$ -bromopropionate is available commercially (Sapon Laboratories,  $n_D^{25}$  1.4452) and is employed without purification. *Bromo esters are severe lachrymators, and operations that involve transferring these compounds from one vessel to another should be conducted in a well-ventilated hood.*

4. If ethyl 4-ethyl-2-methyl-3-hydroxyoctanoate is isolated by distillation of this residue, the yield is about 100 g. (87%), b.p. 122–124°/4.9 mm.,  $n_D^{25}$  1.4415.

5. During heating, the mixture becomes dark brown; however, most of the color is removed by subsequent washing with hydrochloric acid.

If terminal heating is omitted, the yield in the dehydration step is reduced by approximately 15%.

6. If no separation of isomers is required, as when the mixture is to be hydrogenated, the mixed esters may be obtained by distillation; yield, 75–90 g. (71–85%, based on starting aldehyde). It is extremely difficult to separate the  $\Delta^2$ - from the  $\Delta^3$ -ester by fractional distillation, as the two boil only 7° apart; however, by careful fractionation and refractionation through an  $0.8 \times 125$ -cm. simple Podbielniak column with partial-reflux head,<sup>4</sup> it is possible to obtain <sup>3</sup> pure ethyl 4-ethyl-2-methyl-2-octenoate, b.p. 102–103°/4.8 mm.,  $n_D^{25}$  1.4478, and a nearly pure sample of ethyl 4-ethyl-2-methyl-3-octenoate, b.p. 94–95°/4.8 mm.,  $n_D^{25}$  1.4393.

7. When  $\alpha,\gamma$ -dialkyl- $\beta,\gamma$ -unsaturated esters and acids are heated with acid, they are slowly converted to  $\gamma$ -lactones. The corresponding  $\alpha,\beta$ -unsaturated isomers are recovered unchanged.<sup>3</sup> Treating a mixture of the two isomeric esters or acids with sulfuric acid in refluxing glycol thus destroys the unconjugated isomer, while leaving the conjugated compound intact. Whereas the isomeric esters and acids have very similar boiling points (cf. Note 6), the  $\gamma$ -lactone boils 20–25° lower than the  $\Delta^2$ -acid and thus may be separated easily from the acid by fractional distillation. The acid may also be extracted from the lactone with sodium carbonate, or its barium salt may be precipitated by methanolic barium hydroxide.

Lactonization as a means of obtaining  $\Delta^2$ -acid free from  $\Delta^3$ -isomer is useful for unsaturated acids or esters having an  $\alpha$ -alkyl substituent. Conjugated acids or esters without an  $\alpha$ -alkyl substituent undergo acid-catalyzed isomerization to the  $\Delta^3$ -isomer and subsequent lactonization with loss in yield of the  $\Delta^2$ -compound.<sup>5</sup> In the latter case, use may be made of the differential rate either of bromine addition<sup>6</sup> or of esterification<sup>3</sup> for the conjugated and unconjugated compounds as a means of obtaining pure conjugated acid.

8. In the present case, the proportion of  $\Delta^2$ -isomer in the original dehydration mixture may be estimated to be 42% of the total unsaturated esters, while an equilibrium mixture contains about 67% of the conjugated compound.<sup>3</sup> Thus, the amount of conjugated isomer in the mixture may be considerably increased by base-catalyzed isomerization of the unsaturated esters. For other unsaturated esters, both the composition of the dehydration mixture<sup>3,7</sup> and the equilibrium ratio of the two isomers<sup>3,8</sup> vary, depending on the position and

nature of alkyl substituents on the chain, and equilibration is not always desirable. For suitable compounds the following procedure is advantageous; scrupulous protection against moisture is essential.

A 2-l. round-bottomed flask is fitted with a coil condenser (cooling water *inside* the coil) having a large free space in the center and is protected from atmospheric moisture by a calcium chloride tube. The apparatus is dried thoroughly with a Bunsen burner, and 1.5 l. of commercial ethylene glycol is introduced into the flask, together with 50 ml. of diethyl phthalate. The glycol is heated (with salt bath or electric mantle) to a temperature slightly under reflux, the calcium chloride tube is removed, and 50 g. of sodium is added cautiously, in suitable pieces, through the condenser. It is necessary to wait after the addition of each piece, for sodium melts at these temperatures and dissolves in glycol exothermically with vigorous evolution of hydrogen. After all the sodium has been added, the solution is heated for 1 hour under reflux. The condenser is arranged for distillation into a graduated thoroughly dried pressure-equalizing dropping funnel, and, as before, the system is protected by a calcium chloride tube. Heating is resumed, and the first 300 ml. of distilled glycol, which contains any remaining water, is discarded. The separatory funnel is replaced by a 1-l. stainless-steel flask with standard taper joint, which has been thoroughly dried with a burner. In this flask is collected the next 750 ml. of distilled glycol. The condenser and a calcium chloride tube are transferred to the steel flask, the contents are heated to a temperature slightly under boiling, and 57.5 g. of sodium is added in large pieces as before. The residue of unsaturated esters is introduced from a large pipet, a boiling chip is added, and the mixture is heated for 20 hours under reflux. It is then cooled to room temperature and decanted cautiously into a 2-l. round-bottomed flask containing a mixture of 210 ml. of glycol and 70 ml. of concentrated sulfuric acid. To the flask is added an additional 70 ml. of concentrated sulfuric acid, and after the mixture has been heated under reflux for 12 hours it is worked up as described in the final paragraph of the main procedure. Upon fractional distillation of the products, there are obtained 17.5–23.9 g. (19–26%) of 4-ethyl-4-hydroxy-2-methyloctanoic acid,  $\gamma$ -lactone, and 34.1–39.6 g. (38–43%) of 4-ethyl-2-methyl-2-octenoic acid. In this instance, therefore, the yield of  $\Delta^2$ -acid is increased approximately one-third by isomerizing the dehydration products before converting the  $\Delta^3$ -acid to lactone.

9. An  $0.8 \times 125$ -cm. simple Podbielniak column<sup>4</sup> with partial reflux head is a suitable type.

10. An analytical sample of 4-ethyl-4-hydroxy-2-methyloctanoic acid,  $\gamma$ -lactone, has b.p.  $115-117^\circ/4.3$  mm.,  $n_D^{25}$  1.4462.

11. An analytical sample of 4-ethyl-2-methyl-2-octenoic acid has b.p.  $141-142^\circ/4.6$  mm.,  $n_D^{25}$  1.4628.

### 3. Methods of Preparation

The procedure employed has been previously described by Cason and Rinehart,<sup>3</sup> and is a modification of the standard Reformatsky procedure.<sup>9,10</sup> The Reformatsky reaction, which has been reviewed elsewhere,<sup>9</sup> has been widely employed with ketones, somewhat less frequently with aldehydes, and very seldom with  $\alpha$ -alkyl aliphatic aldehydes.

4-Ethyl-2-methyl-2-octenoic acid has been prepared only by this method. An alternate synthesis of  $\alpha$ -alkyl- $\alpha,\beta$ -unsaturated acids proceeds via  $\alpha$ -bromination of the saturated acid, followed by dehydrohalogenation with quinoline at elevated temperatures.<sup>11</sup> The present method is especially well adapted to preparation of  $\alpha,\gamma$ -dialkyl- $\alpha,\beta$ -unsaturated acids.

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<sup>2</sup> *Org. Syntheses*, Coll. Vol. **3**, 627 (1955).

<sup>3</sup> Cason and Rinehart, *J. Org. Chem.*, **20**, 1591 (1955).

<sup>4</sup> Cason and Rapoport, *Laboratory Text in Organic Chemistry*, p. 237, Prentice-Hall, New York, 1950.

<sup>5</sup> Linstead, *J. Chem. Soc.*, **1932**, 115.

<sup>6</sup> Linstead, *J. Chem. Soc.*, **1927**, 355.

<sup>7</sup> Kon and Nargund, *J. Chem. Soc.*, **1932**, 2461.

<sup>8</sup> For a review of references, cf. Adkins, in Gilman's *Organic Chemistry*, 2nd ed., p. 1042, John Wiley & Sons, New York, 1943.

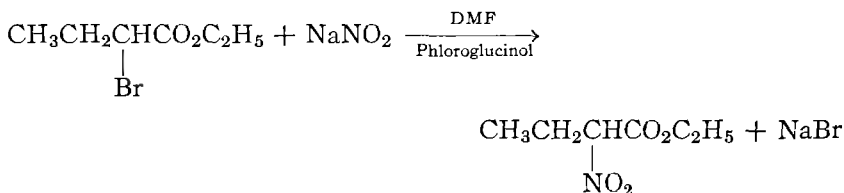
<sup>9</sup> Shriner, *Org. Reactions*, **1**, 2 (1942).

<sup>10</sup> Reference 4, p. 330.

<sup>11</sup> Cason, Allinger, and Allen, *J. Org. Chem.*, **18**, 857 (1953).

## ETHYL $\alpha$ -NITROBUTYRATE

(Butyric acid,  $\alpha$ -nitro-, ethyl ester)



Submitted by NATHAN KORNBLUM and ROBERT K. BLACKWOOD.<sup>1</sup>

Checked by JAMES CASON, JOANNE FACAROS, and WILLIAM G. DAUBEN.

### 1. Procedure

Ethyl  $\alpha$ -bromobutyrate (58.5 g., 0.30 mole) (Note 1) is poured into a stirred mixture of 600 ml. of N,N-dimethylformamide (DMF) (Note 1), 36 g. of sodium nitrite (0.52 mole) (Note 1), and 40 g. of anhydrous phloroglucinol (0.32 mole) (Note 2) contained in a 1-l. three-necked flask equipped with a sealed stirrer. The flask is closed, except for a tube containing calcium chloride, and immersed in a water bath maintained at room temperature (Note 3). Stirring is continued for 2.5 hours (Note 4); then the reaction mixture is poured into 1.2 l. of ice water layered over with 300 ml. of diethyl ether (Note 5). After separation of the upper layer, the aqueous phase is extracted with four 100-ml. portions of ether. The combined extracts are washed with four 100-ml. portions of water and then dried over anhydrous magnesium sulfate. The magnesium sulfate is removed by suction filtration and washed with four 25-ml. portions of ether which are combined with the filtered extract.

The ether is distilled through a small column (Note 6), under reduced pressure, from a 1-l. flask which is heated by a bath whose temperature is gradually raised to about 60°. The residual yellow liquid is transferred, with the aid of a little anhydrous ether, to a 100-ml. flask, and the remaining solvent is distilled through the column under reduced pressure. Rectification of the residue yields 2-3 g. of fore-

run boiling in the range 33–71°/1 mm. which is followed by 33–36 g. (68–75%) of colorless ethyl  $\alpha$ -nitrobutyrate, b.p. 71°/1 mm.,  $n_D^{20}$  1.4233 (Notes 7, 8, and 9).

## 2. Notes

1. The ethyl  $\alpha$ -bromobutyrate employed was redistilled Eastman Kodak white label material, b.p. 64°/15 mm.,  $n_D^{20}$  1.4479. Technical DMF (du Pont) was used, and the sodium nitrite was an analytical grade.

Subsequent to the checking of this preparation, the submitters reported that DMSO (dimethyl sulfoxide) may be a somewhat better solvent for this preparation than is DMF. Since sodium nitrite is more soluble in DMSO, only 250 ml. of this solvent is required for the preparation. The more concentrated solution permits a reduction in reaction time to about 1.5 hours.

2. Ringwood Chemical Corporation technical grade phloroglucinol dihydrate was rendered anhydrous by heating for 3 hours at 110°. By reacting rapidly with any ethyl  $\alpha$ -nitrobutyrate formed, it prevents nitrosation of the  $\alpha$ -nitroester. In the absence of phloroglucinol all of the ethyl  $\alpha$ -nitrobutyrate is destroyed.<sup>2,3</sup>

3. The reaction mixture becomes homogeneous and turns deep red-brown shortly after the addition of the  $\alpha$ -bromoester. The deep color is, presumably, due to nitrosated phloroglucinol; however, this in no way interferes with subsequent isolation of product.

4. Two hours allows more than sufficient time for complete reaction. Since the yield is not critically dependent on this factor, no attempt was made to establish the minimum reaction time. Even after a 17-hour reaction time there is no decrease in yield.

5. Approximately 200 ml. of this ether is required to saturate the aqueous DMF layer.

6. A 60  $\times$  1-cm. externally heated column, packed with 1/8-in. glass helices and equipped with a total reflux variable take-off head, was used by the submitters.

7. Toward the end of the rectification the jacket of the column is heated to 90–95° in order to obtain the last few grams of product.

8. The ethyl  $\alpha$ -nitrobutyrate dissolves rapidly in 10% aqueous sodium hydroxide and dissolves completely in saturated aqueous sodium carbonate on shaking for 2–3 minutes.

9. This procedure has been applied successfully to the synthesis of other  $\alpha$ -nitroesters from  $\alpha$ -bromoesters,<sup>3</sup> as listed below; ethyl bromoacetate is exceptional in that it fails to give ethyl nitroacetate.

SYNTHESIS OF  $\alpha$ -NITROESTERS FROM  $\alpha$ -BROMOESTERS

| $\alpha$ -Nitroester                           | Reaction Time, hr. | Yield, % |
|------------------------------------------------|--------------------|----------|
| Ethyl $\alpha$ -nitropropionate                | 2                  | 62       |
| Ethyl $\alpha$ -nitrocaproate                  | 5                  | 74       |
| Ethyl $\alpha$ -nitroisobutyrate *             | 44                 | 78       |
| Ethyl $\alpha$ -nitroisovalerate               | 150                | 67       |
| Ethyl $\alpha$ -phenyl- $\alpha$ -nitroacetate | 2.5                | 70       |

\* No phloroglucinol employed.

### 3. Methods of Preparation

Ethyl  $\alpha$ -nitrobutyrate may be prepared in 75% yield by the reaction of silver nitrite with ethyl  $\alpha$ -iodobutyrate.<sup>4</sup> It has been prepared in 18% yield by nitration and subsequent decarboxylation of diethyl ethylmalonate.<sup>5</sup> The present method offers the advantage of a direct preparation using sodium nitrite.

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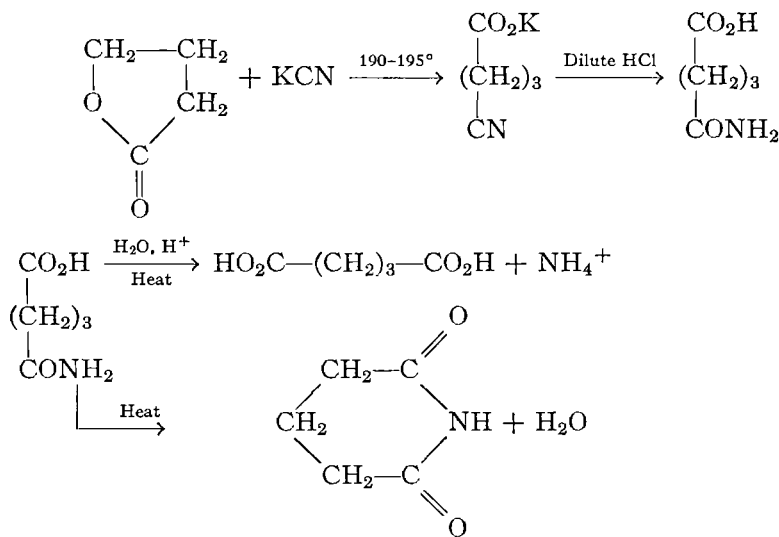
<sup>2</sup> Kornblum, Blackwood, and Mooberry, *J. Am. Chem. Soc.*, **78**, 1501 (1956).

<sup>3</sup> Kornblum, Blackwood, and Powers, *J. Am. Chem. Soc.*, **79**, 2507 (1957).

<sup>4</sup> Kornblum, Chalmers, and Daniels, *J. Am. Chem. Soc.*, **77**, 6654 (1955).

<sup>5</sup> Eicher, Ph.D. Thesis, Purdue University Libraries (1950); Ulpiani, *Atti. reale accad. Lincei*, [5]**13**, II, 346 (1904).

## GLUTARIC ACID AND GLUTARIMIDE



Submitted by G. PARIS, L. BERLINGUET, and R. GAUDRY.<sup>1</sup>  
 Checked by JAMES CASON and EDWIN R. HARRIS.

## 1. Procedure

In a 500-ml. three-necked flask fitted with a sealed mechanical stirrer and a reflux condenser are placed 86 g. (1 mole) of  $\gamma$ -butyrolactone (Note 1) and 72 g. (1.1 moles) of potassium cyanide (Note 2). As the contents of the flask are stirred, the mixture is heated in an oil bath for 2 hours at a temperature of 190–195° (Note 3). There is an initial vigorous reaction which soon subsides. After the completion of the heating period the mixture is cooled to about 100°, and the potassium salt of the cyano acid is dissolved in about 200 ml. of hot water. The warm solution is cautiously acidified to Congo Red by the addition of about 90 ml. of concentrated hydrochloric acid. The resultant solution, which contains glutaric acid monoamide and potassium chloride, is used to prepare glutaric acid or glutarimide.

*Glutaric Acid.* To the solution of monoamide is added 200 ml. of concentrated hydrochloric acid, and the mixture is heated under reflux in the hood for 1 hour. The reaction mixture is evaporated to



dryness under reduced pressure, and the residue is dried by brief heating on a steam bath at reduced pressure. The residual crystalline solid is broken up, ground in a mortar, and extracted with four 200-ml. portions of boiling chloroform. The combined hot extracts are filtered by gravity through a fluted paper on a heated funnel and then concentrated to about 400 ml. After the solution has been cooled in water to effect crystallization, the glutaric acid is collected by suction filtration, washed with cold chloroform, and dried. The yield of slightly discolored glutaric acid, suitable for many purposes, is 105–110 g. (79.5–83.5%), m.p. 95–97°.

If a pure grade of glutaric acid is desired, it is decolorized by boiling for about 1 hour with 10 g. of charcoal in water solution. The charcoal is removed by filtration (Note 4), the water is evaporated under reduced pressure, and the dry residue is recrystallized from chloroform. The yield of white glutaric acid, m.p. 98–99°, is 94–99 g. (71–75%).

*Glutarimide.* The solution containing the monoamide is extracted with six 50-ml. portions of ether. The ether solution is dried over anhydrous sodium sulfate (or by filtering by gravity through a layer of the drying agent), and then the ether is evaporated by heating on a steam bath; the last portion is removed at reduced pressure. The oily residue of glutaric acid monoamide is placed in a 300-ml. round-bottomed flask which is fitted with a bent tube attached to a short condenser, and the flask is immersed in a bath (Note 5) held at 220–225°. Heating is continued until water no longer distills (3–4 hours). The cooled glutarimide is dissolved in about 200 ml. of water, and the solution is boiled for about 30 minutes with about 2 g. of charcoal. The charcoal is removed by filtration, water is removed by distillation at reduced pressure, and the dry residue is crystallized from about 125 ml. of 95% ethanol, with final cooling in an ice bath. The yield of glittering white crystals of glutarimide, m.p. 152–154°, is 65.5–73.5 g. (58–65%) (Note 6).

## 2. Notes

1. Butyrolactone from Eastern Chemical Corporation, 34 Spring Street, Newark 2, New Jersey, was used without purification.

2. Satisfactory results were obtained with potassium cyanide, 96–98% purity, from General Chemical Company or with material indicated as of 95% minimum purity, from Merck & Co., Inc. If

potassium cyanide pellets are used, they should be pulverized before use.

3. Since the reaction mixture is acidified after the heating period, it is most convenient to carry out the reaction in a forced-draft hood in order to provide protection against hydrogen cyanide. If higher temperatures than those specified are used, the reaction may get out of control during the initial vigorous reaction.

4. If filtration by gravity through a fluted paper fails to remove the last traces of charcoal, the filtrate should be refiltered by suction through a thin mat of filter aid such as Supercel.

5. The submitters used an oil bath. The checkers used a salt bath consisting of an equimolar mixture of potassium nitrate and sodium nitrite (Heat Transfer Salt). A salt bath should be handled only with proper precautions, which include wearing goggles and gloves and supporting the bath on a stand bolted to the bench.

6. This material is suitable for preparation of N-bromoglutarimide, as follows. In a 1-l. beaker, provided with a mechanical stirrer, 65 g. of potassium hydroxide is dissolved in 200 ml. of water. The vigorously stirred solution is cooled to about  $-5^{\circ}$ , and as the temperature is maintained below  $0^{\circ}$  there is added gradually 113 g. (1 mole) of glutarimide and cracked ice. To this mixture is added in one portion 160 g. (1 mole) of bromine; then stirring is continued for 1 minute. The mixture is filtered by suction, and the precipitate is dissolved in hot water. On cooling, there crystallizes about 94 g. (49%) of N-bromoglutarimide which melts at about  $165^{\circ}$ . This product is usually suitable for use as a brominating agent. Pure N-bromoglutarimide, m.p.  $180-185^{\circ}$ , is obtained only after several recrystallizations from water.

### 3. Methods of Preparation

Other methods for preparing glutaric acid are cited in previously published procedures for this compound.<sup>2</sup>

Glutarimide has been prepared from glutaric acid and sulfamide<sup>3</sup> or formamide,<sup>4</sup> by distillation of ammonium glutarate,<sup>5</sup> by hydrolysis of pentanedinitrile with acetic acid,<sup>6</sup> and by oxidation of piperidine with hydrogen peroxide.<sup>7</sup>

The present method, based on a recent publication,<sup>8</sup> offers a more convenient synthesis of glutaric acid and its imide, and the method may be readily adapted to a large scale.

<sup>1</sup> Université Laval, Quebec City, Canada.

<sup>2</sup> *Org. Syntheses*, Coll. Vol. 1, 289 (1944); *Org. Syntheses*, **30**, 48 (1950).

<sup>3</sup> Kirsanov and Zolotov, *Zhur. Obshchei Khim.*, **20**, 1145 (1950).

<sup>4</sup> Sugawara and Shigehara, *J. Pharm. Soc. Japan*, **62**, 531 (1942).

<sup>5</sup> Bernheimer, *Gazz. chim. ital.*, **12**, 281 (1882).

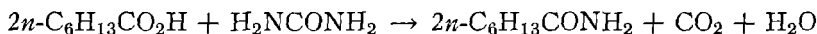
<sup>6</sup> Seldner, *Am. Chem. J.*, **17**, 532 (1895).

<sup>7</sup> Wolfenstein, *Ber.*, **25**, 2777 (1892).

<sup>8</sup> Paris, Gaudry, and Berlinguet, *Can. J. Chem.*, **33**, 1724 (1955).

## *n*-HEPTAMIDE

### (Heptanamide)



Submitted by J. L. GUTHRIE and NORMAN RABJOHN.<sup>1</sup>

Checked by WILLIAM S. JOHNSON and DUANE ZINKEL.

### 1. Procedure

In a 1-l. round-bottomed flask, fitted with a thermometer extending nearly to the bottom, are placed 60 g. (1 mole) of urea and 69 g. (0.5 mole) of 95% *n*-heptanoic acid (Note 1). A condenser (Note 2) is attached to the flask, and the mixture is heated by means of an electric mantle. When the temperature reaches 140°, the urea is in solution, and a rather vigorous evolution of gas occurs which continues for several minutes. The temperature is maintained at 170–180° for 4 hours (Note 3), and then the mixture is allowed to cool.

As soon as the temperature drops to 110–120°, 400 ml. of 5% sodium carbonate solution is added carefully through the condenser, and the mixture is shaken vigorously (Note 4). The mixture is cooled in an ice bath, and the product is collected on a Büchner funnel. The solid, when dry, is slightly colored, and weighs 57–64 g., m.p. 85–91°.

The crude material is boiled for a few minutes with 200 ml. of 95% ethanol and a small amount of decolorizing carbon (Note 5). The mixture is filtered by gravity, and 800 ml. of water is added to the filtrate. The resulting slurry is cooled in an ice-salt bath and the solid is collected by filtration on a Büchner funnel. The product, which is almost colorless, is air-dried. It weighs 44–48 g. (68–74%) and melts at 91–94° (Note 6). Evaporation of the filtrate under reduced pressure and reprecipitation of the residue from 20 ml. of

95% ethanol and 80 ml. of water affords an additional 3–4 g. (5–6%) of material which melts at 90–93°.

## 2. Notes

1. Eastman Kodak Company, yellow label brand (95%), *n*-heptanoic acid was used.

2. A condenser should be chosen which has an inside diameter of at least 1.5 cm.; otherwise frequent loosening of the sublimate is required to prevent clogging. A 3-ft., air-cooled tube with an internal diameter of about 2.5 cm. serves as a satisfactory condenser.

3. Temperatures below 170° lead to slightly lower yields, and temperatures above 180° cause excessive sublimation of urea. Although the reaction is nearly complete after 2 hours, the yield appears to be improved by additional heating.

4. Failure to make the mixture basic leads to the formation of a greasy, colored product.

5. A small amount of solid does not dissolve in the alcohol.

6. Recrystallization from dilute ethanol affords colorless material, m.p. 94–95°.

## 3. Methods of Preparation

Heptamide has been prepared by heating heptanoic acid with ammonia in a sealed tube<sup>2</sup> at 230°, by treating heptanoic anhydride with ammonia,<sup>3</sup> by passing ammonia through heptanoic acid<sup>4</sup> at 125–190°, by the rearrangement of heptaldehyde oxime in the presence of Raney nickel in a quartz tube at 150° for 5 minutes,<sup>5</sup> by the Willgerodt reaction with 2-, 3-, or 4-heptanone or heptanal,<sup>6,7</sup> and by the action of ammonia on heptanoyl chloride.<sup>8</sup>

The procedure described is based on the method of E. Cherbuliez and F. Landolt,<sup>9</sup> by which formic and acetic acids were converted into the corresponding amides.

<sup>1</sup> University of Missouri, Columbia, Missouri.

<sup>2</sup> Hofmann, *Ber.*, **15**, 979 (1882).

<sup>3</sup> Chiozza and Malerba, *Ann.*, **91**, 103 (1854).

<sup>4</sup> Mitchell and Reid, *J. Am. Chem. Soc.*, **53**, 1879 (1931).

<sup>5</sup> Paul, *Bull. soc. chim.*, [54], 1115 (1937).

<sup>6</sup> Cavalieri, Pattison, and Carmack, *J. Am. Chem. Soc.*, **67**, 1783 (1945).

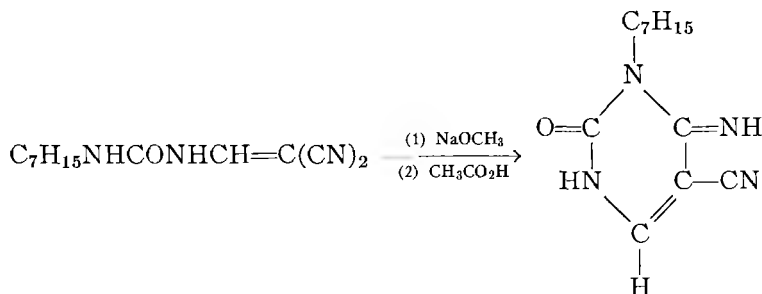
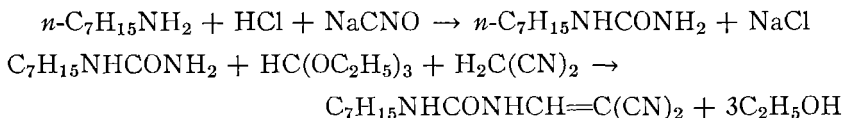
<sup>7</sup> King and McMillan, *J. Am. Chem. Soc.*, **68**, 1369 (1946).

<sup>8</sup> Philbrook, *J. Org. Chem.*, **19**, 623 (1954).

<sup>9</sup> Cherbuliez and Landolt, *Helv. Chim. Acta*, **29**, 1438 (1946).

### 3-*n*-HEPTYL-5-CYANOCYTOSINE

#### [2(1)-Pyrimidone, 3-*n*-heptyl-4(3)-imino-5-cyano]



Submitted by BARBARA B. KEHM and CALVERT W. WHITEHEAD.<sup>1</sup>

Checked by M. S. NEWMAN and K. G. IHRMAN.

### 1. Procedure

A. *N-n*-Heptylurea. To a mixture of 24.1 g. (0.21 mole) of *n*-heptylamine (Note 1), 35 g. of cracked ice, and 150 ml. of ice-cold water is added 38 ml. of 5 *N* hydrochloric acid (Note 2) with stirring. The mixture is heated on the steam bath at 70–80°, and 14.3 g. (0.22 mole) of sodium cyanate is added portion-wise. After 2–4 hours of continued heating, two layers separate. The product crystallizes on standing overnight at room temperature. It is collected on a Büchner funnel, washed with 100 ml. of cold water, and drained as dry as practical by suction. This solid is dissolved in 125 ml. of boiling ethyl acetate, and the resulting solution is cooled to room temperature. The white crystalline *N-n*-heptylurea is filtered and dried on a porcelain plate at room temperature. A yield of 28.5–29.5 g. (86–88%) of product melting at 110–111° is obtained (Note 3).

B. 3-*n*-Heptylureidomethylenemalononitrile. In a 250-ml. round-bottomed flask fitted with a heating mantle and a reflux condenser are placed 28.5 g. (0.18 mole) of *N-n*-heptylurea, 11.9 g. (0.18 mole)

of malononitrile (Note 4), and 26.7 g. (0.18 mole) of triethyl orthoformate (Note 4). The mixture is heated under reflux for 2 hours and then cooled in ice. The solid product is collected by suction filtration on a Büchner funnel. The filtrate is concentrated on the steam bath to incipient crystallization, cooled, and filtered. The two lots of tan solid, 41–42 g., thus obtained are dissolved in 75 ml. of 75% ethyl alcohol in a 250-ml. beaker, 2 g. of decolorizing carbon is added, and the mixture is boiled for 2–3 minutes with constant stirring (necessary to avoid vigorous bumping). The hot solution is filtered by gravity into a 250-ml. Erlenmeyer flask through fluted filter paper. The flask is stoppered and cooled in the refrigerator for 4 hours. The solid product is collected by suction filtration on a Büchner funnel and washed four times with 10-ml. portions of distilled water. The white crystalline 3-*n*-heptylureidomethylenemalononitrile is dried at 50° in a vacuum oven. It melts at 130–132° and amounts to 33.8–34.8 g. (80–83%) (Note 5).

C. *3-n-Heptyl-5-cyanocytosine*. In a 250-ml. Erlenmeyer flask are placed 33.8 g. (0.145 mole) of 3-*n*-heptylureidomethylenemalononitrile and 70 ml. of methanol; then 8.5 g. (0.16 mole) of sodium methoxide (Note 6) is added carefully in small portions (Note 7). The resulting solution is allowed to stand at room temperature for 3 days in the stoppered flask. The contents of the flask are dissolved in 300 ml. of cold water in an 800-ml. beaker, and the solution is stirred as 11 ml. of glacial acetic acid is added. The precipitated solid is collected by suction filtration on a Büchner funnel and washed with three 40-ml. portions of distilled water. The undried product is dissolved in 600 ml. of hot ethyl alcohol; then the solution is filtered into a 1-l. flask by gravity through a fluted filter paper, concentrated on the steam bath to 200 ml., and cooled in the refrigerator for 4 hours. The 3-*n*-heptyl-5-cyanocytosine crystallizes in white needles, melts at 192–197° (Note 8), and amounts to 29.7–31.1 g. (88–92%) (Note 9).

Recrystallization of 20 g. of this product from 230 ml. of hot ethyl alcohol affords 17.8 g. of fine colorless needles, m.p. 199.5–202.5°.

## 2. Notes

1. *n*-Heptylamine is available from Sapon Laboratories, 543 Union Street, Brooklyn 15, New York, and from Distillation Products Industries, Rochester 3, New York.

2. If excess acid is present, considerable foaming may occur on addition of sodium cyanate.

3. The melting point for *N-n*-heptylurea given in the literature<sup>2</sup> is 110–111°.

4. Commercially available reagents were employed.

5. The melting point for *n*-heptylureidomethylenemalononitrile is reported<sup>3</sup> to be 130–132°. An additional 1–1.5 g. may be obtained by evaporating the filtrate to a volume of 100 ml.

6. Solid sodium methoxide is available from Mathieson Chemical Corporation, Niagara Falls, New York. Alternately a solution prepared by dissolving 3.6 g. of sodium in 70 ml. of methanol may be used.

7. Upon addition of solid sodium methoxide to the methanol solution considerable heat is evolved.

8. The melting point of 3-*n*-heptyl-5-cyanocytosine is given in the literature<sup>4</sup> as 200°.

9. The submitters obtained comparable yields in all steps using 144.2 g. (1.25 moles) of heptylamine and correspondingly larger amounts of all reagents.

### 3. Methods of Preparation

*N-n*-heptylurea has been prepared by the action of nitrourea on *n*-heptylamine.<sup>5</sup>

3-*n*-Heptyl-5-cyanocytosine has been prepared by a variation of this procedure by Whitehead.<sup>4</sup>

The procedure described here has given equally good yields of other 3-alkyl-5-cyanocytosines and 3-cycloalkyl-5-cyanocytosines; however, it does not yield 3-aryl-5-cyanocytosines from arylureas.

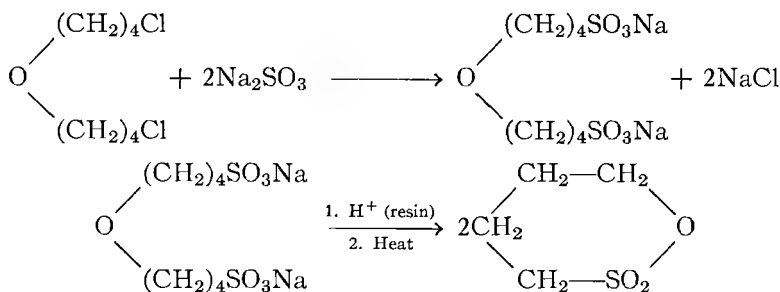
<sup>1</sup> Eli Lilly & Company, Indianapolis, Indiana.

<sup>2</sup> Forselles and Wahlforss, *Ber.*, **25** Referate, 636 (1892).

<sup>3</sup> Whitehead, *J. Am. Chem. Soc.*, **75**, 674 (1953).

<sup>4</sup> Whitehead and Traverso, *J. Am. Chem. Soc.*, **77**, 5871 (1955).

<sup>5</sup> Tseng and Ho, *J. Chinese Chem. Soc.*, **4**, 335 (1936) [*C. A.*, **31**, 1011 (1937)].

**4-HYDROXY-1-BUTANESULFONIC ACID SULTONE****(1-Butanesulfonic acid, 4-hydroxy-,  $\delta$ -sultone)**Submitted by A. O. SNODDY.<sup>1</sup>

Checked by T. L. CAIRNS and W. R. BRASEN.

**1. Procedure**

A mixture of 132.5 g. (1.05 moles) of sodium sulfite, 99.5 g. (0.5 mole) of bis-4-chlorobutyl ether (Note 1), and 450 ml. of water is placed in a creased 1-l. three-necked flask fitted with an efficient sealed stirrer and a reflux condenser. The third neck of the flask is closed with a stopper, and the mixture is heated and stirred vigorously under reflux until the ether has dissolved (Note 2). At the end of this time, heating is discontinued, and 60 ml. of concentrated c.p. hydrochloric acid is cautiously added to the solution. The mixture is then boiled with stirring until sulfur dioxide is no longer evolved. Solid barium chloride dihydrate (or a 10% aqueous solution of this salt) is added to the hot solution (Note 3) until all sulfate has been precipitated; then the barium sulfate is removed by suction filtration through a layer of filter aid.

The filtered solution is diluted to 2 l. with water and passed through a column of ion-exchange resin (Notes 4 and 5). A test portion of the effluent should yield no ash on evaporation and ignition of the residue. The column is washed with water until the effluent is no longer acid to litmus, and the washings are added to the original eluent. The total eluent is evaporated (Note 6) at reduced pressure (water aspirator) until the volume is about 250 ml.; then it is transferred to a



500-ml. pot which is equipped for vacuum distillation and attached to a short Vigreux column. After most of the remaining water and hydrochloric acid have been removed at the pressure obtainable with an aspirator, an oil pump is attached (Note 7), and the heating bath is cautiously raised to a temperature in the range 130–150°. The distillate is allowed to stand in a separatory funnel until the layers have separated (several hours may be required), then the crude sultone is withdrawn and distilled (Note 8) at reduced pressure. The yield of sultone, b.p. 134–136°/4 mm., is 99–109 g. (72–80%),  $n_D^{25}$  1.4619–1.4625,  $d_4^{25}$  1.3347, m.p. 12.5–14.5°.

## 2. Notes

1. Material supplied by Matheson, Coleman and Bell was used without purification.

2. This reaction may be carried out under pressure in a rocking autoclave at 180° in about 8 hours. When it is carried out under reflux with vigorous stirring in a creased flask it is complete in about 20 hours, whereas 50–60 hours are required if an ordinary flask is used.

3. Any sulfate ions resulting from oxidation of sulfite should be removed; otherwise they will be converted to sulfuric acid in the subsequent procedure and destroy sultone. Ordinarily, 12–13 g. of barium chloride dihydrate is required. The end point of the addition is conveniently determined with tetrahydroquinone indicator used in spot tests on filter paper [cf. *Ind. Eng. Chem., Anal. Ed.*, **9**, 331 (1937)].

4. Rohm & Haas Amberlite IR-120, which has been developed with 3 *N* hydrochloric acid and then washed free from chlorides with water, is used in the form of a column 6 cm. in diameter and 55 cm. in length. Such a column contains approximately 1.1 kg. of resin (50% moisture) and is equivalent to about 2.2 moles of hydrogen chloride.

5. The checkers found that the procedure of Helberger and Lanterman,<sup>2</sup> which avoids the use of an ion-exchange resin, is also satisfactory in case it is regarded as inconvenient to set up the resin column. According to this procedure, after completion of the reaction with sodium sulfite, anhydrous hydrogen chloride is passed into the hot solution to liberate sulfur dioxide. After removal of sulfate as in the described procedure, the undiluted aqueous solution is saturated with hydrogen chloride gas at a temperature below 25°. The precipitated sodium chloride is removed by suction filtration, the filter cake is

washed with two 50-ml. portions of 12 *N* hydrochloric acid, and then the combined filtrate and washings are worked up as described for the eluent from the resin column.

6. The checkers found that satisfactory results may also be obtained if the water is evaporated by heating the solution on a steam bath as air is aspirated through it.

7. At the bath temperature specified, and low pressure, dehydration and distillation occur; if a pressure of about 4 mm. is maintained, the vapor temperature is in the range 132–138°. The temperature of the bath should be raised slowly and with caution, or else the contents of the pot may froth through the column into the distillate. The receiver should be cooled in a Dry Ice-acetone bath to prevent vapors from reaching the oil pump.

8. Water is nearly insoluble in the sultone. The small amount of water and a very volatile impurity which are present in the crude sultone distil rapidly before the sultone is collected. An efficient cold trap should be used to protect the pump from the volatile materials.

### 3. Methods of Preparation

4-Hydroxy-1-butanefulfonic acid sultone has been made through the chlorosulfonation of 1-chlorobutane,<sup>3</sup> from 4-chlorobutyl acetate<sup>2,4</sup> which is prepared through the reaction of tetrahydrofuran and acetyl chloride,<sup>2</sup> from 4-chlorobutanol,<sup>4</sup> and from bis-4-chlorobutyl ether.<sup>2</sup> Both 4-chlorobutanol and bis-4-chlorobutyl ether can be prepared from tetrahydrofuran.<sup>5</sup>

The described procedure is based on the method of Helberger and Lanterman.<sup>2</sup>

<sup>1</sup> The Procter & Gamble Company, Miami Valley Laboratories, Cincinnati 31, Ohio.

<sup>2</sup> Helberger and Lanterman, *Ann.*, **586**, 158 (1954).

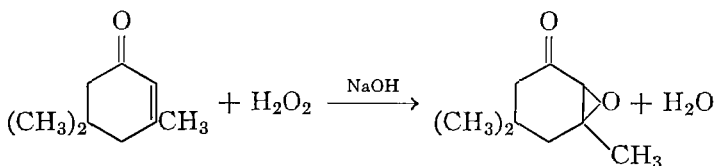
<sup>3</sup> Helberger, Manecke, and Fischer, *Ann.*, **562**, 23 (1949); Helberger, Manecke, and Heyden, *Ann.*, **565**, 22 (1949).

<sup>4</sup> Truce and Hoerger, *J. Am. Chem. Soc.*, **76**, 5357 (1954).

<sup>5</sup> *Org. Syntheses*, **30**, 27 (1950).

## ISOPHORONE OXIDE

(Cyclohexanone, 2,3-epoxy-3,5,5-trimethyl-)

Submitted by RICHARD L. WASSON and HERBERT O. HOUSE.<sup>1</sup>

Checked by JAMES CASON and RALPH J. FESSENDEN.

## 1. Procedure

In a 1-l. three-necked flask, equipped with a dropping funnel, a mechanical stirrer, and a thermometer, is placed a solution of 55.2 g. (0.4 mole) of isophorone (Note 1) and 115 ml. (1.2 moles) of 30% aqueous hydrogen peroxide (*Caution! avoid contact with skin*) in 400 ml. of methanol. After the contents of the flask have been cooled to 15° by means of an ice bath, 33 ml. (0.2 mole) of 6 *N* aqueous sodium hydroxide is added, dropwise and with stirring, over a period of 1 hour. During the addition the temperature of the reaction mixture is maintained at 15–20° with a bath of cold water (Note 2). After the addition is complete, the resulting mixture is stirred for 3 hours as the temperature of the reaction mixture is maintained at 20–25° (Notes 3 and 4). The reaction mixture is then poured into 500 ml. of water, and the resulting mixture is extracted with two 400-ml. portions of ether. The combined extracts are washed with water and dried over anhydrous magnesium sulfate. After the bulk of the ether has been removed by distillation (or flash distillation) through a 30-cm. Vigreux column (Note 5) at atmospheric pressure, the residual liquid is distilled through the Vigreux column under reduced pressure. The yield of isophorone oxide (Note 4) is 43–44.5 g. (70–72%), b.p. 70–73°/5 mm.,  $n_D^{25}$  1.4500–1.4510.

## 2. Notes

1. A technical grade of isophorone, b.p. 80–84°/9 mm.,  $n_D^{25}$  1.4755, purchased from Eastman Kodak Company, was employed for this preparation.

2. If the temperature of the reaction mixture is less than  $15^{\circ}$ , the reaction does not begin. When the resulting mixture is subsequently warmed to room temperature the exothermic reaction which results is difficult to control (Note 3).

3. If the temperature of the reaction mixture is allowed to rise above  $30^{\circ}$ , the yield of isophorone oxide is diminished.

4. If desired, the course of the reaction may be followed by means of the optical density of the reaction mixture at  $235\text{ m}\mu$ . The ultraviolet spectrum of isophorone has a maximum at  $235\text{ m}\mu$  ( $\epsilon$  13,300); the ultraviolet spectrum of isophorone oxide has a maximum at  $292\text{ m}\mu$  ( $\epsilon$  43). A total reaction time of 4 hours under the conditions specified was found to be ample for the complete conversion of isophorone to its oxide. If the conversion is not complete, the product cannot be separated from the unchanged isophorone without recourse to precise fractional distillation. The absence of isophorone from the final product may be verified by examination of the spectrum at  $235\text{ m}\mu$ .

5. When the checkers distilled the product through a simple type of Podbielniak column of 65-cm. length, with heated jacket and partial reflux head, the boiling range was  $1^{\circ}$ ,  $74\text{--}75^{\circ}/6\text{ mm.}$ , but the yields and index of refraction were the same as those reported by the submitters.

### 3. Method of Preparation

Isophorone oxide has been prepared by the epoxidation of isophorone with alkaline hydrogen peroxide.<sup>2,3</sup>

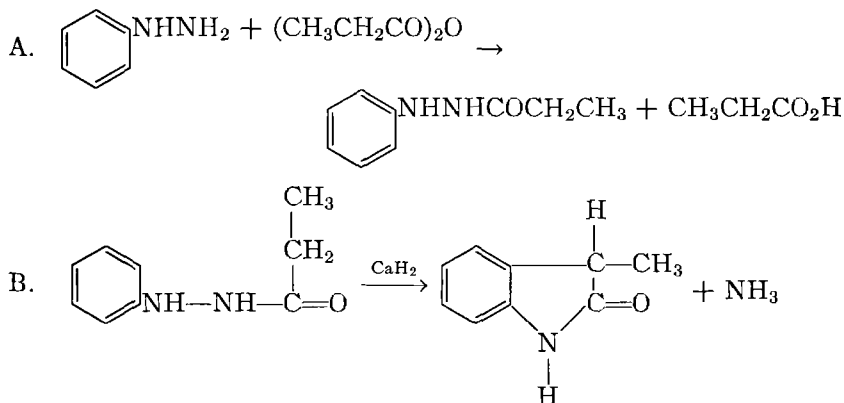
<sup>1</sup> Massachusetts Institute of Technology, Cambridge 39, Massachusetts.

<sup>2</sup> Treibs, *Ber.*, **66**, 1483 (1933).

<sup>3</sup> House and Wasson, *J. Am. Chem. Soc.*, **79**, 1488 (1957).

## 3-METHYLOXINDOLE

(Oxindole, 3-methyl-)

Submitted by ABRAHAM S. ENDLER and ERNEST I. BECKER.<sup>1</sup>

Checked by JAMES CASON and WARREN N. BAXTER.

## 1. Procedure

A. *β-Propionylphenylhydrazine*. To 130 g. (1.0 mole) of propionic anhydride (Note 1), contained in a 500-ml. wide-mouthed Erlenmeyer flask which is cooled in an ice bath, there is added slowly with swirling 108 g. (1.0 mole) of phenylhydrazine (Note 1) at such a rate that the maximum temperature does not exceed 60°. After addition is complete, the flask is corked (not so tightly as to give a vacuum which may collapse the flask) and allowed to stand 72 hours at room temperature. At the end of this period, the resultant solid cake is broken up and slurried with 100 ml. of toluene. The suspension is cooled to 5° in an ice bath; then the product is collected by suction filtration and washed with 200 ml. of a mixture of equal parts of cyclohexane and toluene, precooled to 5°. The yield of vacuum-dried, almost white crystals, m.p. 158–159°, is 140–145 g. (85–88%).

B. *3-Methyloxindole*. A mixture of 33 g. (0.20 mole) (Note 2) of *β*-propionylphenylhydrazine and 14 g. (0.33 mole) of freshly ground commercial calcium hydride (Note 3) is placed in a 500-ml. round-bottomed flask, which is equipped with a 15-cm. air condenser of

2.5 cm. diameter. The flask is immersed to two-thirds its depth in an oil bath, in a forced-draft hood, and the bath is heated, cautiously as 190° is approached. In the range 190–215°, a very vigorous exothermic reaction sets in (sometimes after a brief delay), and considerable gas and vapor is expelled through the air condenser. The vigorous reaction abates in 5 minutes or less, and the oil bath is raised to about 230°. After heating at this temperature has been continued for 30 minutes, the flask is removed from the bath and cooled to room temperature.

A mixture of 50 ml. of methanol and 20 ml. of water is cautiously added to the cooled reaction mixture, and this is followed by slow addition of concentrated hydrochloric acid (Note 4) until the *pH* is brought to 1–2 (Hydriion test paper). When effervescence has stopped, 50 ml. of water is added, and the contents of the flask are boiled gently for 1 hour. Additional concentrated hydrochloric acid is added as needed to maintain the specified *pH* (Note 5). At this point, all solid material should have been decomposed. The mixture is transferred to a 600-ml. beaker, using 10 ml. of methanol to wash out the flask, sufficient sodium hydroxide is added (Note 6) to bring the *pH* to about 3 (Hydriion test paper or more accurately with methyl orange indicator), and water is added to bring the volume to about 300 ml. The mixture is stirred in an ice bath until the oily layer solidifies, and the crude crystalline material is collected by suction filtration at about 15° and washed with 100 ml. of water. After vacuum drying at 70°, the yield of crude product is 16–19 g., but this material should be purified before further use.

The crude product is distilled in a short-path distillation apparatus composed of a 125-ml. Claisen flask connected by a ground-glass joint to a receiver which is a 300-ml. round-bottomed flask with side tubulature for evacuation. A 50-g. portion (Note 7) of crude 3-methyloxindole is placed in the distillation flask, which is completely immersed in an oil bath. The product is collected at approximately 132°/1.5 mm. The solid distillate is dissolved in 75 ml. of hot methanol, then 25 ml. of hot water is added. After crystallization has been continued for 24 hours at about 20°, there is obtained 35–37 g. (41–44% from  $\beta$ -propionylphenylhydrazine) of light-yellow crystals, m.p. 122.5–123.5° (softening at 121.5°) (Note 8). Five grams of less pure material is recoverable from the mother liquor and may be distilled with a succeeding batch.

## 2. Notes

1. Phenylhydrazine and propionic anhydride from Fisher Scientific Company were used without purification by the submitters. The checkers distilled the propionic anhydride before use, since old samples contained considerable propionic acid.

2. The ring closure is so highly exothermic that runs no larger than that described are recommended. Several lots may be combined for distillation, as suggested in the description.

3. The checkers used 40-mesh calcium hydride, from Metal Hydrides, Inc. The submitters report that there may also be used freshly ignited lime (22 g., 0.39 mole), but with a reduction of 10–20% in the yield.

4. The amount of concentrated hydrochloric acid is usually 40 ml. or more, depending on the quality of the calcium hydride.

5. This procedure is for the purpose of hydrolyzing unchanged starting material.

6. The final pH is brought to about 3 in order to minimize the solubility of 3-methyloxindole in strong acid without precipitating the phenylhydrazine which is present at this point.

7. The checkers obtained the same yields when the product of a single ring closure was distilled and crystallized.

8. After two crystallizations from butanol and two from toluene, the product may be obtained in about 25% recovery as white crystals of m.p. 123.8–124.6°.

## 3. Methods of Preparation

3-Methyloxindole has been prepared by the reduction of  $\alpha$ -(2-nitrophenyl)propionic acid,<sup>2</sup> by heating  $\beta$ -propionylphenylhydrazine with lime<sup>3</sup> or with sodium alkoxides,<sup>4</sup> and by reduction of the benzoyl derivative of oxindole-3-aldehyde.<sup>5</sup>

<sup>1</sup> Department of Chemistry, Polytechnic Institute of Brooklyn, Brooklyn, New York.

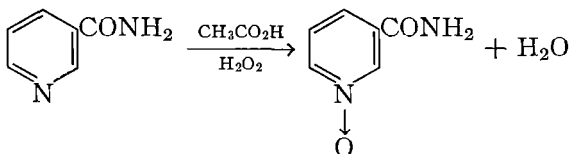
<sup>2</sup> Trinius, *Ann.*, **227**, 274 (1885).

<sup>3</sup> Brunner, *Monatsh.*, **18**, 533 (1897).

<sup>4</sup> C. F. Boehringer and Söhne (Waldhof b. Mannheim), Ger. pat. 218,727, Kl. 12p., Jan. 10, 1910 [*Friedlander*, **9**, 968 (1908–1910)].

<sup>5</sup> L. Horner, *Ann.*, **548**, 134 (1941).

## NICOTINAMIDE-1-OXIDE



Submitted by E. C. TAYLOR, JR.,<sup>1</sup> and ALDO J. CROVETTI.<sup>2</sup>

Checked by CHARLES C. PRICE and WALTER A. SCHROEDER.

### 1. Procedure

In a 2-l. round-bottomed flask with ground-glass joint (Note 1) are placed 100 g. (0.82 mole) of powdered nicotinamide (Note 2) and 1 l. of C.P. glacial acetic acid, and the mixture is warmed with occasional shaking on a steam bath until a clear solution is obtained. To this mixture is added 160 ml. (1.39 moles) of cold 30% hydrogen peroxide. An air condenser is attached to the reaction flask, and the mixture is heated on a steam bath for 3.5 hours.

The reaction mixture is then distilled under reduced pressure (80–100 mm.) (Note 3). After 600–700 ml. has distilled, the mixture is diluted with 150–200 ml. of distilled water and the distillation is continued. The product separates near the end of the distillation, causing somewhat vigorous bumping for a short period. When the bumping has almost ceased, the pressure is reduced to 20 mm. and the distillation continued almost to dryness (Note 4).

The major portion of wet solid is removed from the flask and transferred to a 1-l. Erlenmeyer flask. The remaining solid is washed out with a little distilled water, and the washings are transferred to the flask. The solid is dissolved in the smallest amount of boiling water required, the flask removed from the heat source, and 50 ml. of ethyl alcohol added (Note 5). The flask is allowed to cool slowly, and, after the major portion of the product has separated, the flask is cooled to 5° overnight. The solid is removed by filtration and washed with cold alcohol, then acetone, and finally ether. The white, crystalline, air-dried product weighs 82–93 g. (73–82%), m.p. 291–293° dec. (rapid heating); the compound starts to turn brown at about 280–285° (Note 6).



## 2. Notes

1. Since hydrogen peroxide attacks rubber stoppers, glass-jointed equipment is recommended.

2. U.S.P. Niacinamide (Mallinckrodt) was used.

3. For the distillation, the still head consisted of a Claisen-type adapter with a parallel side arm (24/40 standard taper joints), 21 cm. high and 10.5 cm. wide. An ordinary straight still head is attached to the parallel side arm. This large still head prevents any bumping solid from entering the condenser.

4. Distilling to complete dryness exposes the solid to prolonged heating and causes oxidation of the product, which is obtained colored and in lower yield.

5. The alcohol serves to retain the brown color upon recrystallization and to decompose any excess hydrogen peroxide.

6. Because of the questionable value of the melting point as a criterion of purity, the checkers analyzed two samples of the product: Calcd. for  $C_6H_6N_2O$ : C, 52.17; H, 4.34. Found (Sample 1): C, 52.34; H, 4.44. Found (Sample 2): C, 52.61, 52.63; H, 4.46, 4.53.

## 3. Methods of Preparation

The procedure given is essentially that described by Taylor and Croveti.<sup>3</sup> Nicotinamide-1-oxide (m.p. 275–276° dec.) has also been prepared by the alkaline hydrolysis of nicotinonitrile-1-oxide<sup>4</sup> and by the action of ammonium hydroxide on methyl nicotinate-1-oxide.<sup>5</sup> The melting point of the product prepared by the latter synthesis is reported to be 282–284° dec.

<sup>1</sup> Frick Chemical Laboratory, Princeton University, Princeton, New Jersey.

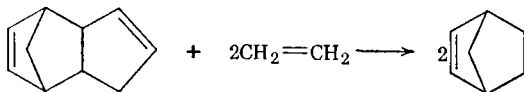
<sup>2</sup> Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois.

<sup>3</sup> Taylor and Croveti, *J. Org. Chem.*, **19**, 1633 (1954).

<sup>4</sup> Jujo, *J. Pharm. Soc. Japan*, **66**, 21 (1946) [*C. A.*, **45**, 6200 (1951)].

<sup>5</sup> Shimizu, Naito, Ohta, Yoshikawa, and Dohmori, *J. Pharm. Soc. Japan*, **72**, 1474 (1952) [*C. A.*, **47**, 8077 (1953)].

**NORBORNYLENE**  
**(Bicyclo[2.2.1]hept-2-ene)**



Submitted by J. MEINWALD and N. J. HUDAK.<sup>1</sup>

Checked by J. D. ROBERTS, C. M. SHARTS, and W. G. WOODS.

### 1. Procedure

A 1-l. steel bomb is charged with 200 g. (1.51 moles) of dicyclopentadiene (Note 1). The bomb is flushed with ethylene (Note 2) and then filled while shaking to an initial pressure of 800–900 p.s.i. at 25°. Shaking is continued as the bomb is slowly heated (Note 3) to 190–200° and maintained at this temperature for 7 hours (Note 4). At the end of this period, the reaction vessel is cooled and vented, and the crude product is transferred into a simple distillation apparatus (Note 5). A fraction boiling between 93° and 100° is collected, yield 162–202 g. (57–71%, based on dicyclopentadiene) (Note 6). The norbornylene may be redistilled with negligible losses to give a final product, b.p. 94–97°/740 mm., m.p. 44–44.5° (sealed capillary).

### 2. Notes

1. The dicyclopentadiene used by the submitters was supplied by the Enjay Company. No preliminary purification is required. Technical (85%) dicyclopentadiene has been found by the checkers to give 54–56% yields of norbornylene without preliminary purification.

2. C.P. grade ethylene was obtained from the Matheson Company.

3. To avoid complications due to the exothermic nature of this reaction,<sup>2</sup> a rate of heating of about 50° per hour was adopted (cf. Note 6).

4. Near 180°, the maximum pressure (about 2350 p.s.i.) is developed.

5. In spite of the low melting point of norbornylene, the product has a remarkable tendency to crystallize. Care should therefore be taken

to prevent premature solidification of the distillate. A short-path, air-cooled assembly using rather wide-diameter tubing is convenient for this purpose.

6. The submitters report the same yields using a 3-l. bomb and 3.68 moles of dicyclopentadiene. Larger-scale preparations may necessitate special control procedures.

### 3. Methods of Preparation

The procedure described above is essentially that of Thomas.<sup>2</sup> Norbornylene has also been prepared by the addition of ethylene to monomeric cyclopentadiene<sup>3</sup> [*Org. Syntheses*, **32**, 41 (1952)], by dehydration of  $\beta$ -norborneol with phosphorus pentoxide,<sup>4</sup> and by dehydrohalogenation of norbornyl chloride or bromide using quinoline.<sup>4,5</sup>

<sup>1</sup> Department of Chemistry, Cornell University, Ithaca, New York.

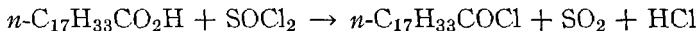
<sup>2</sup> Thomas, *Ind. Eng. Chem.*, **36**, 310 (1944); Thomas and Universal Oil Products, U. S. pat. 2,340,908 [*C. A.*, **38**, 4273 (1944)].

<sup>3</sup> Joshel and Butz, *J. Am. Chem. Soc.*, **63**, 3350 (1941).

<sup>4</sup> Komppa and Beckmann, *Ann.*, **512**, 175 (1934).

<sup>5</sup> Alder and Rickert, *Ann.*, **543**, 10 (1940).

## OLEOYL CHLORIDE



Submitted by C. F. H. ALLEN, J. R. BYERS, JR., and W. J. HUMPHLETT.<sup>1</sup>

Checked by MAX TISHLER and R. CONNELL.

### 1. Procedure

Seventy grams (0.25 mole) of oleic acid (Note 1) is placed in the dropping funnel *H* of the tangential apparatus (Fig. 2; Note 2). The thionyl chloride distillation is started and regulated (Note 2); the upper part of the column should be filled with the vapor, and reflux should be constant and steady. The acid is dropped in at the top of the column over a period of 35 minutes (120 g. per hour). The product that collects in the receiver *I* contains about 25–27% of thionyl chloride (Note 2) if the heated lower leg *K* is employed. The product in

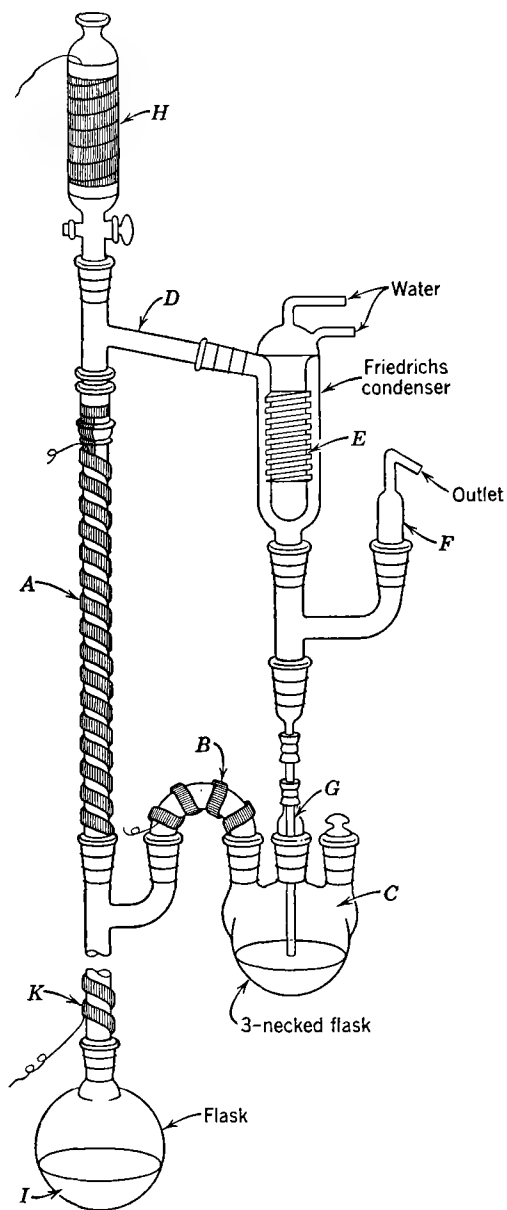


FIG. 2.

receiver *I* is heated on a steam bath under reduced pressure until the more volatile components are completely removed. The residue of crude acid chloride weighs 72–74 g. (97–99% yield). The infrared spectrum of this product shows no trace of a carboxyl band (Notes 1, 3, and 4).

The crude acid chloride will serve for most purposes. It can be distilled at very low pressures (b.p. 99–109°/25  $\mu$ ) to yield a water-white product;  $n_D^{25}$  1.4580–1.4613 (Note 5). Small amounts of oleoyl chloride may be distilled at higher pressures; b.p. 180–185°/1–2 mm. The infrared absorption curve of the oleic acid obtainable by hydrolysis is the same as that of the oleic acid used; thus no isomerization during the reaction is indicated.

## 2. Notes

1. The oleic acid used by the submitters had a freezing point of  $-2^\circ$  to  $+13^\circ$  and a boiling point of 182–187°/1–2 mm. It was a 90% middle cut from Emerson 233 as obtained from Emery Industries, Inc., Cincinnati, Ohio. The checkers found that the amount of color in the product was a function of the purity of the oleic acid. The product from distilled Emerson 233 was dark red-brown, whereas that from a purified grade of oleic acid was pale yellow.

2. The tangential apparatus<sup>2</sup> is built from stock pieces of glassware having 24/40 standard taper glass joints, and it is clamped to two ring stands. The reactor consists of a column 50 cm. long and 2 cm. inside diameter, packed with  $\frac{1}{8}$ -in. glass helices of the type used for packing distillation columns, and wrapped with a 275-watt flexible heating tape *A*, 6 ft. long and  $\frac{1}{2}$  in. wide, with lead wires connected to a variable transformer such as the Powerstat or Variac, which is attached to a source of 110-volt power. Near the bottom of the column is a heated side arm connection *B* to a three-necked flask reservoir *C*. The use of the leg *K*, wrapped with a heating tape, removes much of the excess of thionyl chloride and is particularly advantageous with acid chlorides (such as oleoyl chloride) that are sensitive to heat. The crude effluent from the reactor ordinarily contains 40–50% of thionyl chloride, which is reduced one-half or more by this leg. It is not essential for use with chlorides insensitive to heat. Vapor supplied by boiling the liquid in the reservoir is forced to circulate via *B* through the column by sufficient heat input to the column and the lower leg

*K*; the excess escapes at the top through the side arm *D* which is connected to a Friedrichs condenser *E*. The bottom of the condenser is connected to a Y-shaped section with an outlet *F* for effluent gas and a return *G* which extends below the surface of the liquid in the reservoir. At the top of the column is a 250-ml. dropping funnel *H* for admitting reactants to the column. Since oleic acid is a liquid at room temperature, heating of this funnel is not required in the present preparation. At the bottom of the column is a 500-ml. flask *I* for receiving the product.

3. Other acid chlorides can be prepared similarly. (a) Palmitoyl chloride: Palmitic acid is a solid at room temperatures (m.p. 61–62°) and is not sufficiently soluble in palmitoyl chloride or thionyl chloride, and so these cannot be used as solvents. It is admitted to the reactor in the melted condition by warming the acid in the dropping funnel *H*. The quality of the chloride naturally depends on the homogeneity of the starting acid; palmitic acid usually contains a little stearic acid, which does not affect the melting point. Palmitoyl chloride,  $n_D^{25}$  1.4489, can be obtained as a water-white product by distillation at very low pressures (b.p. 110°/15–24  $\mu$ ), or with negligible decomposition at boiling points as high as 165°.

(b) Ricinoleoyl chloride: b.p. 205–210°/8 mm., 125–130°/25  $\mu$ ;  $n_D^{25}$  1.4759; this substance decomposes significantly at the higher distillation temperature.

(c) 2,4-Di-*tert*-amylphenoxyacetyl chloride: In this instance, the corresponding solid acid (20 g.) is dissolved in the acid chloride (80 g.) as a solvent and admitted at the rate of 70 g. of acid per hour. The crude acid chloride, after removal of the excess thionyl chloride, contains about 1% of unchanged acid (infrared determination). The yield of distilled acid chloride, b.p. 143–146°/2 mm.,  $n_D^{25}$  1.5062, is 85%.

4. The described procedure is not suitable for all acids. For instance, the acid chloride must not have a boiling point so near that of thionyl chloride that they are inseparable by distillation. Certain high-molecular-weight acids give dehydration products, presumably diketenes: e.g., behenic and dihydroxystearic acids.

5. The refractive index will vary with the purity of the oleic acid. Oleic acid purified by low-temperature crystallization and by conversion into the oleic acid-urea complex (95.3% oleic, 0.7% linoleic) yielded a product with  $n_D^{25}$  1.4613.

### 3. Methods of Preparation

This modification of the continuous reactor (cf. benzoylacetanilide, p. 2) with countercurrent distillation is preferred for reactions in which a large amount of solvent or excess of one reactant is essential, but increase of total volume is undesirable. It is especially useful if the substances involved are heat-sensitive; with this apparatus the reactants are heated for only a few minutes at most. It is particularly applicable to the preparation of acid chlorides from carboxylic acids and thionyl chloride (cf. Notes 3 and 4). An indefinite amount of product can be prepared by replenishing the reactants as they are consumed.

Oleoyl chloride has been prepared by treatment of oleic acid with thionyl chloride,<sup>3</sup> phosphorus trichloride or pentachloride, and oxalyl chloride.<sup>4</sup> The highest yield (86%) reported was secured by use of oxalyl chloride in carbon tetrachloride, but the more economical phosphorus trichloride gave a yield of 60%. The standard procedures for obtaining aliphatic acid chlorides have been described many times without inclusion of details other than physical properties. Only references to the procedures useful in the laboratory are given.

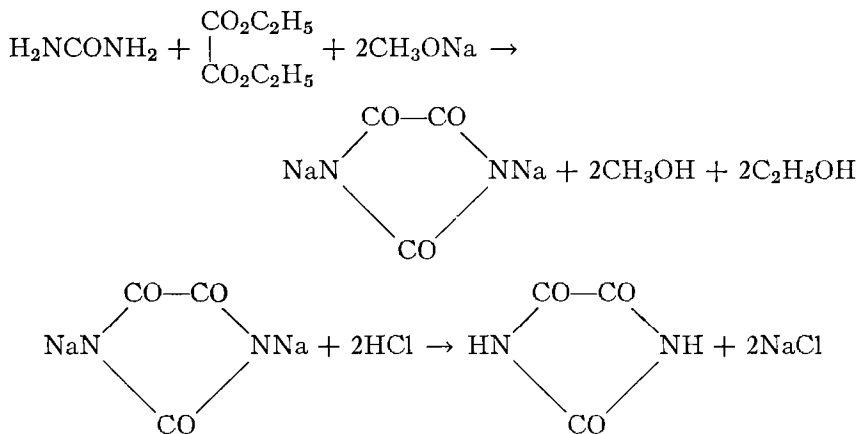
<sup>1</sup> Eastman Kodak Company, Rochester, New York.

<sup>2</sup> Allen, Byers, Humphlett, and Reynolds, *J. Chem. Educ.*, **32**, 394 (1955).

<sup>3</sup> Verkade, *Rec. trav. chim.*, **62**, 393 (1943); Fierz-David and Kuster, *Helv. Chim. Acta*, **22**, 82 (1939).

<sup>4</sup> Bauer, *Oil and Soap*, **23**, 1 (1946).

## PARABANIC ACID

Submitted by JOSEPH I. MURRAY.<sup>1</sup>

Checked by M. S. NEWMAN and TADAMICHI FUKUNAGA.

## 1. Procedure

Eight hundred fifty milliliters of absolute methanol (magnesium-dried) is distilled directly, through a condenser, into a 1-l. three-necked reaction flask equipped with a sealed mechanical stirrer and an efficient reflux condenser protected by a drying tube. After about 300 ml. of methanol has been distilled, the drying tube is removed from the reflux condenser, and small pieces of clean sodium are added to the stirred methanol at such a rate that the alcohol vapors do not escape from the condenser (Note 1). When a total of 23 g. (1 g. atom) of sodium has been added, the drying tube is replaced, the distillation of methanol is completed (Note 1), and the system is brought to a temperature of 20–25° (other temperatures are less favorable). The inlet condenser is removed, 30 g. (0.5 mole) of dry finely ground urea (Note 2) is quickly added to the reaction mixture, and the opening is then closed by attaching a dropping funnel. When the urea has dissolved completely, the addition of 70 g. (0.48 mole) of diethyl oxalate (Note 2) is begun (Note 3). A white precipitate forms immediately.



Stirring is continued for 1 hour after the addition of the ester is completed (Note 4). One hundred milliliters of concentrated hydrochloric acid is added dropwise to the mixture at a rate that causes little increase in the solution temperature, stirring is continued for a few minutes, and the mixture is filtered. The residue is washed twice with a small quantity of methanol, and the filtrate and washings are transferred to a 2-l. two-necked flask equipped with a sealed stirrer and a vacuum take-off. The alcohol is removed under the reduced pressure of a good water aspirator (Note 5). The practically dry solid residue is washed from the evaporator with water which is used as the recrystallization solvent (Note 6). When the bulk of the solid has dissolved, the solution is cooled slightly below the boiling point, 2 g. of activated carbon is added, and the solution is filtered through a hot Büchner funnel by use of moderate suction. The solution yields a white, crystalline precipitate of parabanic acid upon standing in a refrigerator overnight. The yield of purified, dried product melting at 241–243° with decomposition is 39–41.5 g. (71.5–76%).

## 2. Notes

1. The checkers used Mallinckrodt analytical reagent methanol without drying and distilling. The sodium was added to 300 ml. of the methanol, and the remainder of the methanol was added dropwise. The results obtained in this way were the same as those described by the submitter.

The hydrogen released during the formation of the sodium methoxide prevents moisture from entering the system. More rapid addition of the sodium and reduced loss of methanol vapor are realized if the reaction flask is surrounded by an ice bath during the addition of the metal. Calcium chloride should not be used in the drying tube because of possible clogging. Drierite ( $\text{CaSO}_4$ ) is preferable.

2. The checkers used reagent grade urea (Baker) and diethyl oxalate (Matheson, Coleman and Bell), without purification.

3. Ester addition must be quite slow (2 drops per second or less) to prevent emulsion formation and extremely low yields.

4. At the end of 1 hour, the precipitated salt should be in a fine crystalline form which settles readily when the stirring is momentarily stopped. A viscous, creamy suspension which is poorly mixed by the stirring usually gives poor yields. Factors contributing to this condi-

tion have been found to be: insufficient amount of solvent initially, too rapid addition of ester, and improper temperature control.

5. Considerable frothing may be encountered during the first stages of the evaporation, particularly when a steam bath is used to hasten removal of the solvent. Rapid stirring helps to cut down frothing and lessens bumping.

6. The solid may go into solution rather slowly even in boiling water.

### 3. Methods of Preparation

Parabanic acid can be prepared by the condensation of urea with diethyl oxalate in an ethanolic solution of sodium ethoxide,<sup>2</sup> by reaction of urea with an ethereal solution of oxalyl chloride,<sup>3</sup> by oxidizing uric acid with an acid solution of perhydrol,<sup>4</sup> or by the action of hot, concentrated nitric acid on uric acid.<sup>5</sup> The present method gives better yields than the previously reported methods and is better adapted to larger-scale preparations.

<sup>1</sup> Department of Chemistry, University of Buffalo, Buffalo, New York.

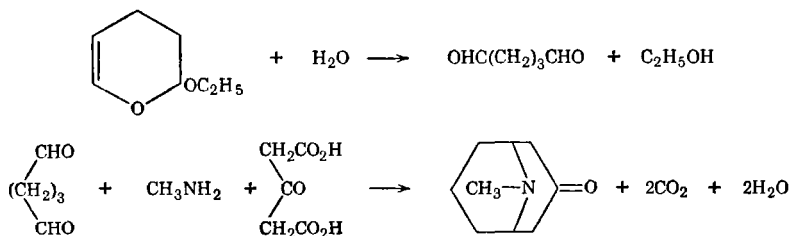
<sup>2</sup> Michael, *J. prakt. Chem.*, [2]**35**, 457 (1886).

<sup>3</sup> Biltz and Topp, *Ber.*, **46**, 1387 (1913).

<sup>4</sup> Biltz and Schiemann, *Ber.*, **59**, 721 (1926).

<sup>5</sup> Behrend and Asche, *Ann.*, **416**, 226 (1918).

### PSEUDOPELLETIERINE



Submitted by ARTHUR C. COPE, HUGH L. DRYDEN, JR., and CHARLES F. HOWELL.<sup>1</sup>

Checked by N. J. LEONARD, D. F. MORROW, and W. D. SMART.

### 1. Procedure

In a 3-l. round-bottomed flask equipped with a mechanical stirrer and flushed with a slow stream of nitrogen are placed 22 ml. (0.26

mole) of concentrated hydrochloric acid (sp. gr. 1.18), 165 ml. of "deoxygenated" water (Note 1), and 64 g. (0.5 mole) of 2-ethoxy-3,4-dihydro-2H-pyran (b.p. 62–65°/50 mm.,  $n_D^{25}$  1.4378) (Note 2). The mixture is stirred vigorously for 20 minutes and then allowed to stand for 1 hour.

To the resulting colorless solution of glutaraldehyde are added, in order, 350 ml. of water, 50 g. (0.74 mole) of commercial methylamine hydrochloride dissolved in 500 ml. of water, 83 g. (0.57 mole) of acetonedicarboxylic acid (Note 3) dissolved in 830 ml. of water, and a solution of 88 g. (0.25 mole) of disodium hydrogen phosphate dodecahydrate and 7.3 g. (0.18 mole) of sodium hydroxide dissolved in 200 ml. of water by heating. Carbon dioxide is evolved, and the pH of the solution, initially 2.5, increases to 4.5 after the mixture has been stirred under nitrogen for 24 hours. Concentrated hydrochloric acid (33 ml.) is added, and the solution is heated on the steam bath for 1 hour to complete the decarboxylation (Note 4). After the solution has been cooled to room temperature, 75 g. of sodium hydroxide in 100 ml. of water is added (Note 5), and the basic mixture is extracted with eight 250-ml. portions of methylene chloride (Note 6). The combined methylene chloride extracts are dried over sodium sulfate, concentrated to about 500 ml. (Note 7), and filtered through a layer of 400 g. of alumina (Note 8) packed in a 50-mm. column. The column is eluted with methylene chloride until about 1.5 l. of eluate has been collected. The eluate is concentrated under reduced pressure to yield crystalline but yellow pseudopelletierine. The solid is sublimed at 40° and 0.3 mm. to yield 47–55.5 g. (61–73%) of crude, nearly colorless pseudopelletierine (Note 9). The product is dissolved in 100 ml. of boiling pentane, 3 ml. of water is added, and the mixture is boiled until the aqueous layer disappears. After thorough chilling in a refrigerator, the crystals which separate are collected on a filter and washed well with ice-cold pentane. Evaporation of the combined filtrate and washings to 20 ml., followed by filtration and washing, yields a second crop of almost equally pure material. The combined pseudopelletierine hemihydrate weighs 47–55 g. and melts at 47–48.5°. Sublimation of the hemihydrate as described above removes the water of hydration and yields 44–52 g. (58–68%) of pure, colorless pseudopelletierine, m.p. 63–64° (sealed tube). Anhydrous material which has been prepared in this manner does not decompose on storage under dry conditions.

## 2. Notes

1. "Deoxygenated" water is prepared by passing a stream of nitrogen through ordinary distilled water and is used throughout the preparation until the condensation is completed. The use of ordinary distilled water may lower the yield by no more than a few per cent.

2. This compound is prepared by the addition of ethyl vinyl ether to acrolein, under conditions similar to those described for a similar addition of methyl vinyl ether to crotonaldehyde in *Org. Syntheses*, **34**, 29 (1954); see Longley and Emerson, *J. Am. Chem. Soc.*, **72**, 3079 (1950). Glutaraldehyde is available currently as a 30% aqueous solution from the Carbide and Carbon Chemicals Company, 30 East 42nd Street, New York.

3. The preparation of acetonedicarboxylic acid is described in *Org. Syntheses*, Coll. Vol. 1, 10 (1941). The acid may also be obtained from Chas. Pfizer & Company, 630 Flushing Avenue, Brooklyn 6, New York.

4. Omission of the decarboxylation step decreases the yield of crude material to 57%. The temperature should reach about 80°.

5. The pH rises to about 12. A lower pH allows extraction of more of the dark-brown resin. The extraction must be performed promptly since the product can undergo self-condensation at this pH.

6. The employment of ether instead of methylene chloride requires the use of a continuous extractor for 2 days.

7. The checkers found that the purification of the pseudopelletierine could be simplified, at least in those preparations in which commercial acetonedicarboxylic acid was used. Thus, the crude product obtained by evaporation to dryness of the methylene chloride extracts can be sublimed directly. Two sublimations give pseudopelletierine of m.p. 62–64°, in 58–62% yield, comparable to the product obtained after the more extended purification procedure described in the text.

8. Chromatographic alumina (400 g.) is treated with 500 ml. of ethyl acetate at room temperature. After 48 hours, the alumina is collected on a filter and washed first with 1 l. of distilled water and then with 1 l. of methanol. After drying in air, the alumina is activated by heating at 120° for 3 hours at 50–100 mm.

9. Resublimation directly may serve for the final purification (see Note 7). Distillation is inconvenient because of the tendency of pseudopelletierine to crystallize in the condenser. The distilled product darkens rather rapidly even in the cold and melts at 47–53°. The

once sublimed product also darkens slowly even when kept under dry nitrogen in a refrigerator. If anhydrous pseudopelletierine is exposed to moist air, the hemihydrate is formed, m.p. about 48°.

### 3. Methods of Preparation

Pseudopelletierine has been obtained from the bark of the pomegranate tree (*Punica granatum* L.).<sup>2-5</sup> The synthesis of the alkaloid from glutaraldehyde, methylamine, and calcium acetonedicarboxylate was first achieved by Menzies and Robinson.<sup>6</sup> The synthetic method subsequently was improved by Schöpf and Lehmann,<sup>7</sup> and others.<sup>8,9</sup> The condensation of a dialdehyde with an amine and acetonedicarboxylic acid to form a heterobicyclic compound (an alkaloid or alkaloid analog, usually employing mild or so-called "physiological" conditions) is sometimes referred to as a Robinson-Schöpf synthesis.

The experimental procedure described is essentially one reported by Ziegler and Wilms<sup>8</sup> as subsequently modified,<sup>9</sup> except that the glutaraldehyde is prepared from 2-ethoxy-3,4-dihydro-2H-pyran instead of cyclopentene ozonide<sup>8</sup> or pyridine via dihydropyridine and glutaraldehyde dioxime.<sup>9</sup> Essentially these procedures have also been reported briefly by other investigators.<sup>10</sup>

<sup>1</sup> Massachusetts Institute of Technology, Cambridge 39, Massachusetts.

<sup>2</sup> Tanret, *Compt. rend.*, **88**, 716 (1879); **90**, 696 (1880).

<sup>3</sup> Piccinini, *Gazz. chim. ital.*, **29**, II, 311 (1899).

<sup>4</sup> Hess and Eichel, *Ber.*, **50**, 1386 (1917); **52**, 1005 (1919).

<sup>5</sup> Chaze, *Compt. rend. soc. biol.*, **118**, 1065 (1935).

<sup>6</sup> Menzies and Robinson, *J. Chem. Soc.*, **125**, 2163 (1924).

<sup>7</sup> Schöpf and Lehmann, *Ann.*, **518**, 1 (1935).

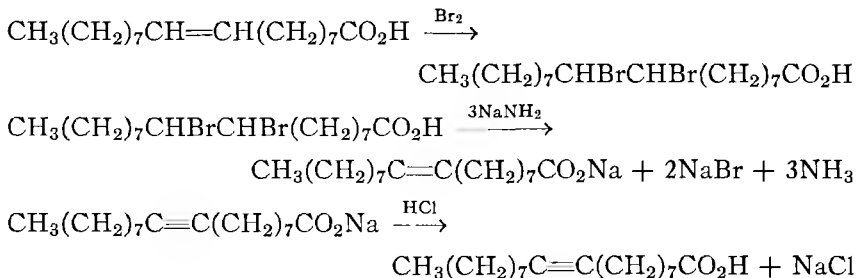
<sup>8</sup> Ziegler and Wilms, *Ann.*, **567**, 31 (1950).

<sup>9</sup> Cope, Dryden, Overberger, and D'Addieco, *J. Am. Chem. Soc.*, **73**, 3416 (1951).

<sup>10</sup> Alder and Dortmann, *Ber.*, **86**, 1544 (1953).

## STEAROLIC ACID

## (9-Octadecynoic acid)



Submitted by N. A. KHAN, F. E. DEATHERAGE, and J. B. BROWN.<sup>1</sup>

Checked by MAX TISHLER, W. J. PALEVEDA, and E. F. SCHOENEWALDT.

## 1. Procedure

Bromine is added dropwise with stirring to a solution of 100 g. (0.35 mole) of oleic acid of at least 95% purity (Note 1) in 400 ml. of dry ether maintained at 0–5°, until the color of bromine persists. About 53 g. (0.33 mole) of bromine is needed; the excess is removed by addition of a few drops of oleic acid.

The sodamide required for dehydrobromination is prepared<sup>2</sup> in a 5-l. three-necked flask fitted with a sealed Hershberg stirrer, a gas inlet tube, and a large cold-finger condenser charged with Dry Ice-acetone. The condenser outlet is connected to a safety trap followed by a bubbler tube containing concentrated aqueous ammonia. Liquid ammonia (1.9 l., Note 2) is introduced into the flask through the inlet tube (*Hood!*); then 1.6 g. of anhydrous ferric chloride (C.P., black) is added in one portion with vigorous stirring. After 5–10 minutes, 3 g. of metallic sodium is dropped into the brown solution to convert the iron salt into the catalytic form. After the evolution of hydrogen has ceased, the remainder of the sodium (total 43 g., 1.87 g. atoms) is added in small pieces with continued stirring. Gray, grainy crystals of sodamide settle out as the reaction proceeds.

The ethereal solution of dibromostearic acid, prepared as described above, is introduced slowly from a dropping funnel into the reaction flask. After the reaction has been allowed to proceed for 6 hours with

continuous stirring, 60 g. of solid ammonium chloride (1.12 moles) is added in portions to destroy excess sodamide. The ammonia is allowed to evaporate until there remains a dry-appearing solid, and then 1 l. of water is added. The mixture is warmed to 60–70° under nitrogen (Note 3) and acidified by the addition of an excess (50 ml.) of concentrated aqueous hydrochloric acid. The aqueous layer is removed by siphoning, and the organic layer is washed with four 500-ml. portions of hot (60°) water. The aqueous layer is separated each time by siphoning. After the fourth washing, the oily product is solidified by cooling the flask in an ice bath, and the residual water is drained off. The crude product is dried on the steam bath under vacuum (Note 4).

The crude acid is dissolved in 500 ml. of petroleum ether at room temperature. The small amount of amorphous solid which may separate is removed by filtration through Supercel, and the filtrate is concentrated under reduced pressure to 300 ml. Chilling to 0–5° yields a first crop of tan crystals which is collected by suction filtration and washed with the minimum amount of ice-cold petroleum ether. Concentration of the mother liquors to 150 ml. and chilling yields a second crop of brownish crystals. The combined crops are dissolved in 300 ml. of petroleum ether, and the light-red solution is chilled to 0–5°. The almost white to light-tan crystals are collected, washed with a small amount of cold petroleum ether, and dried in a vacuum desiccator. There is obtained 51.5–61.5 g. (51–61%) of stearolic acid, m.p. 46–46.5° (Note 5).

## 2. Notes

1. Oleic acid of acceptable purity may be prepared from olive oil fatty acids by the method of Brown and Shinowara,<sup>3</sup> Wheeler and Riemenschneider,<sup>4</sup> Brown and Foreman,<sup>5</sup> or Khan, Deatherage, and Brown.<sup>6</sup> It may also be purchased from the Hormel Institute, Austin, Minnesota.

2. Experience has shown that about 5 g. atoms of sodium should be used for each mole of oleic acid used as starting material. For each gram atom of sodium, 0.8–1.0 g. of ferric chloride, 1 l. of liquid ammonia, and 0.5–0.7 mole of ammonium chloride are necessary. The sodamide reaction proceeds best in comparatively dilute liquid ammonia solution.

3. The liquid stearolic acid is highly susceptible to autoxidation in the presence of air,<sup>7</sup> and this portion of the work-up should be conducted in a nitrogen atmosphere.

4. Alternatively, the product obtained after acidification may be taken up in ether, and the ether extract washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure. This procedure is reported by the submitters to be more convenient for preparations on a smaller scale, and to give a slightly improved yield.

5. This stearolic acid has been thoroughly characterized <sup>6</sup> by the freezing-point curve, ultraviolet and infrared spectra, ozonization, and hydrogenation. It has been shown to be free both of positional isomers and of olefinic acids such as oleic and elaidic acids. Its properties include: m.p. 46–46.5°, iodine number (Wijs titration, 30 minutes) 89.5,  $n_D^{54.5}$  1.4510,  $n_D^{61.5}$  1.4484, neutral equivalent 279.2–279.6 (theory 280.4), hydrogen uptake 95–100% of theory for a triple bond. The last trace of color is difficult to remove by recrystallization from petroleum ether. It can be removed, however, by crystallization from a 20–30% solution in acetone at –5 to –8°, or from an 8–10% solution at –20°, or by distillation (b.p. 189–190°/2mm.).

### 3. Methods of Preparation

Nearly all methods for preparation of stearolic acid involve dehydrohalogenation of a 9,10-dihalostearic acid, or its esters, with alcoholic potassium hydroxide; the most recent method is that of Adkins and Burks.<sup>8</sup> These methods employ drastic conditions, which result in poorer yields than those obtainable on dehydrohalogenation with sodamide.<sup>6</sup> Methyl 9,10-dibromostearate, on dehydrobromination with sodamide, yields stearolamide <sup>6</sup> (m.p. 82–83°) which may be hydrolyzed to stearolic acid. For preparative purposes, however, this method offers no special advantage over that described here.

<sup>1</sup> The Ohio State University, Columbus, Ohio.

<sup>2</sup> Greenlee and Henne, *Inorg. Syntheses*, **2**, 128 (1946).

<sup>3</sup> Brown and Shinowara, *J. Am. Chem. Soc.*, **59**, 6 (1937).

<sup>4</sup> Wheeler and Riemenschneider, *Oil and Soap*, **16**, 207 (1939).

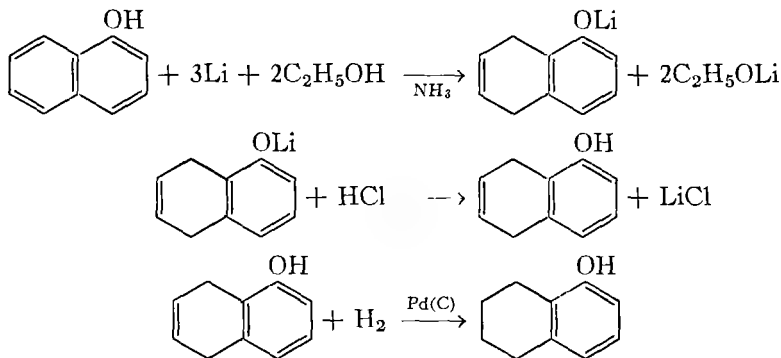
<sup>5</sup> Foreman and Brown, *Oil and Soap*, **21**, 183 (1944).

<sup>6</sup> Khan, Deatherage, and Brown, *J. Am. Oil Chemists Soc.*, **28**, 27 (1951).

<sup>7</sup> Khan, Brown, and Deatherage, *J. Am. Oil Chemists Soc.*, **28**, 105 (1951).

<sup>8</sup> *Org. Syntheses*, Coll. Vol. **3**, 785 (1955).



***ar*-TETRAHYDRO- $\alpha$ -NAPHTHOL****(1-Naphthol, 5,6,7,8-tetrahydro-)**Submitted by C. DAVID GUTSCHE and HUGO H. PETER.<sup>1</sup>

Checked by JOHN C. SHEEHAN, GEORGE H. BUCHI, and DWAIN M. WHITE.

**1. Procedure**

A 3-l. three-necked flask, equipped with a Dry Ice condenser (Note 1), a sealed Hershberg-type stirrer, and an inlet tube, is set up in a hood and charged with 108 g. (0.75 mole) of  $\alpha$ -naphthol (Note 2). The stirrer is started, and to the rapidly stirred flask contents (Note 3) is added 1 l. of liquid ammonia as rapidly as possible (about 5 minutes). When the naphthol has gone into solution (about 10 minutes), 20.8 g. (3.0 g. atoms) of lithium metal (Note 4) is added in small pieces and at such a rate as to prevent the ammonia from refluxing too violently (Note 5). After the addition of the lithium has been completed (about 45 minutes), the solution is stirred for an additional 20 minutes and is then treated with 170 ml. (3.0 moles) of absolute ethanol which is added dropwise over a period of 30–45 minutes (Note 6). The condenser is removed, stirring is continued, and the ammonia is evaporated in a stream of air introduced through the inlet tube. The residue is dissolved in 1 l. of water, and, after the solution has been extracted with two 100-ml. portions of ether, it is carefully acidified with concentrated hydrochloric acid. The product formed is taken into ether with three 250-ml. extractions, and then the ether extract is washed with water and dried over anhydrous sodium sulfate. The ether is removed

by evaporation to yield 106–108 g. (97–99%) of crude 5,8-dihydro-1-naphthol, m.p. 69–72°. This material is dissolved in 250 ml. of ethyl acetate and hydrogenated with 3.0 g. of 10% palladium on charcoal catalyst (Note 7) at 2–3. atm. pressure in a Parr apparatus until the theoretical amount of hydrogen has been absorbed (about 45 minutes). The catalyst is removed by filtration, and the solvent is removed by distillation to leave 105–107 g. of an oil which quickly solidifies, m.p. 67–69.5°. Recrystallization from 250 ml. of petroleum ether (b.p. 88–98°) gives 93–97 g. (84–88%) of almost colorless crystals, m.p. 68–68.5°.

## 2. Notes

1. A cold-finger type of condenser approximately 10 × 40 cm. is satisfactory.

2. Eastman's white label  $\alpha$ -naphthol or equivalent is the most satisfactory starting material. Technical-grade  $\alpha$ -naphthol may be used, but it gives an inferior product that is difficult to purify.

3. Rapid stirring during the addition of the ammonia is necessary to prevent the formation of a hard cake and resultant interference with the stirrer.

4. Lithium metal strip (Metalloy Corporation, Rand Tower, Minneapolis, Minnesota) is wiped to remove the protective grease and then placed in petroleum ether (b.p. 32–37°). Pieces are cut with scissors, air-dried to remove solvent, and added to the reaction mixture.

5. During the addition of the lithium the solution turns deep blue. After this has occurred (after about one-third of the lithium has been added), the rate of addition can be increased considerably.

6. Toward the end of the addition of the alcohol, foaming may occur but may be subdued by reducing the rate of stirring.

7. See Mozingo [*Org. Syntheses*, Coll. Vol. 3, 686 (1955)] for the preparation of this catalyst.

## 3. Methods of Preparation

ar-Tetrahydro- $\alpha$ -naphthol has been prepared by sodium and amyl alcohol reduction of  $\alpha$ -naphthylamine followed by diazotization and hydrolysis,<sup>2,3</sup> by sodium and amyl alcohol reduction of  $\alpha$ -naphthol,<sup>4-6</sup> by sulfonation of tetralin followed by sodium hydroxide fusion,<sup>7</sup> and by catalytic reduction of  $\alpha$ -naphthol.<sup>8</sup> ar-Dihydro- $\alpha$  naphthol has

been prepared by reduction of  $\alpha$ -naphthol with sodium and alcohols<sup>9</sup> and with sodium and ammonia.<sup>10</sup> The use of lithium in related systems has been investigated and provides the basis for the preparation described.<sup>11</sup>

<sup>1</sup> Washington University, St. Louis, Missouri.

<sup>2</sup> Bamberger and Althausse, *Ber.*, **21**, 1893 (1888).

<sup>3</sup> Green and Rowe, *J. Chem. Soc.*, **113**, 955 (1918).

<sup>4</sup> Bamberger and Bordt, *Ber.*, **23**, 215 (1890).

<sup>5</sup> Jacobson and Turnbull, *Ber.*, **31**, 897 (1898).

<sup>6</sup> Bachmann and Ness, *J. Am. Chem. Soc.*, **64**, 536 (1942).

<sup>7</sup> Schroeter, *Ann.*, **426**, 83 (1922).

<sup>8</sup> Musser and Adkins, *J. Am. Chem. Soc.*, **60**, 664 (1938).

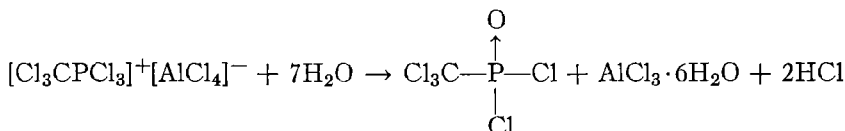
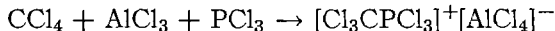
<sup>9</sup> Rowe and Levin, *J. Chem. Soc.*, **119**, 2021 (1921).

<sup>10</sup> Birch, *J. Chem. Soc.*, **1944**, 430.

<sup>11</sup> Wilds and Nelson, *J. Am. Chem. Soc.*, **75**, 5360 (1953).

## TRICHLOROMETHYLPHOSPHONYL DICHLORIDE

(Trichloromethylphosphonic dichloride)



Submitted by KENNETH C. KENNARD and CLIFF S. HAMILTON.<sup>1</sup>

Checked by JOHN C. SHEEHAN and J. L. YEH.

### 1. Procedure

*Caution! This preparation should be conducted in a hood.*

In a 2-l. round-bottomed three-necked flask, fitted with an efficient reflux condenser, mechanical stirrer, and dropping funnel (Note 1), are placed 133.3 g. (1 mole) of anhydrous powdered aluminum chloride, 137.4 g. (1 mole) of phosphorus trichloride, and 184.6 g. (1.2 moles) of carbon tetrachloride (Note 2). The reactants are stirred slowly until they are thoroughly mixed, and then heat is applied carefully until the reaction begins. At this point the liquid boils vigorously, and the reaction mixture becomes thicker so that faster stirring is necessary. Finally, the stirrer is stopped when the

mixture becomes solid. After the reaction has cooled for 30 minutes, 1 l. of methylene chloride is run into the flask (Note 3), and the solvent is stirred vigorously until the solid is finely suspended (Note 4). The reflux condenser is replaced by a low-temperature thermometer which dips into the reaction mixture, the suspension is cooled in a Dry Ice-acetone bath, and the temperature is kept at  $-10$  to  $-20^{\circ}$  as distilled water (180 g., 10 moles) is added dropwise with vigorous stirring over a period of about 25 minutes (Note 5). After the water addition is complete, stirring is continued for 15 minutes without the cold bath.

The apparatus is dismantled, and the reaction mixture is filtered quickly by suction through a 1.5-cm. layer of filter aid on an 11-cm. Büchner funnel placed on a 2-l. filter flask. The filter cake is pressed down well and washed with three 50-ml. portions of methylene chloride. The filtrate is immediately protected from moisture by calcium chloride tubes, and the solvent is removed by distillation from a 2-l. flask. After the solution has been concentrated to about 225 ml., the hot liquid is poured into a suitable container (Note 6), and the remaining solvent is removed under reduced pressure (Note 7). The yield is 192–199 g. (81–84%) of a white, crystalline solid which melts at  $155$ – $156^{\circ}$ .

## 2. Notes

1. The equipment is dried and protected from atmospheric moisture by calcium chloride tubes.
2. It is important that the reactants are pure; otherwise the complex is colored. C.P. reagents are satisfactory provided the containers are freshly opened.
3. The methylene chloride must be redistilled from aluminum chloride to prevent coloration of the product.
4. If the solid adheres to the flask, the flask is heated lightly with a free flame to loosen it.
5. Vigorous stirring is necessary to prevent caking of the aluminum chloride hydrate and to prevent localized hydrolysis. The checkers found that exactly 7 moles of water gave a somewhat improved yield, but handling was more difficult.
6. The submitters used a 500-ml. round-bottomed wide-mouthed flask.
7. The product may be warmed to aid solvent removal, but it is decomposed by prolonged heating above  $60^{\circ}$ .

### 3. Methods of Preparation

The aluminum chloride process <sup>2,3</sup> is a general method for the preparation of alkylphosphonyl dichlorides. The procedure described here is essentially that of Kennard and Hamilton <sup>4</sup> and is based on the procedure of Kinnear and Perren.<sup>2</sup>

<sup>1</sup> University of Nebraska, Lincoln, Nebraska.

<sup>2</sup> Kinnear and Perren, *J. Chem. Soc.*, **1952**, 3437.

<sup>3</sup> Clay, *J. Org. Chem.*, **16**, 892 (1951).

<sup>4</sup> Kennard and Hamilton, *J. Am. Chem. Soc.*, **77**, 1156 (1955).

## SUBJECT INDEX

*(This cumulative index comprises material from Volumes 30-37; for previous volumes see Collective Volumes 1, 2, and 3.)*

Names in small capital letters refer to the titles of individual preparations. A number in ordinary bold-face type denotes the volume. A page number in bold-face italics indicates that the detailed preparative directions are given or referred to, entries so treated include principal products and major by-products, special reagents or intermediates (which may or may not be isolated), compounds mentioned in the text or Notes as having been prepared by the method given, and apparatus described in detail or illustrated by a figure. Page numbers in ordinary type indicate pages on which a compound or subject is mentioned in connection with other preparations. For example, Allylbenzene, **31**, **85**, **86**, indicates that allylbenzene is mentioned on page 85, and that directions for its preparation are given on page 86, of Volume 31.

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Library of Congress Catalog Card Number: 21-17747

PRINTED IN THE UNITED STATES OF AMERICA

## NOMENCLATURE

Preparations appear in the alphabetical order of common names of the compounds. For convenience in surveying the literature concerning any preparation through *Chemical Abstracts* subject indexes, the *Chemical Abstracts* indexing name for each compound is given as a subtitle if it differs from the common name used as the title.

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Additions, corrections, and improvements to the preparations previously published are welcomed and should be directed to the Secretary.

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AN ANNUAL PUBLICATION OF SATISFACTORY  
METHODS FOR THE PREPARATION  
OF ORGANIC CHEMICALS

VOLUME 37

1957

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